보건학박사 학위논문

A Genome-Wide Search for Gene-by-Environment Interactions on Dyslipidemia and Hypertension: Genetic Interactions with Cigarette Smoking, Alcohol Consumption, and Obesity

이상지질혈증 및 고혈압에 대한 전장유전체에서의
유전자-환경 상호작용 연구: 흡연 및 음주, 비만을 중심으로

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Abstract

Introduction: Many human traits or complex diseases are known to result from the combined effect of genes, environmental factors, and interactions of them. Gene-by-environment interactions (GxEs) may hold the key to further insights on the biology of disease and the development of better prediction models, particularly when genes interacting with modifiable environmental factors are investigated at a genome-wide level. Dyslipidemia and hypertension, one of the most prevalent chronic diseases for Koreans, are well-established risk factors for cardiovascular disease (CVD). Several studies on the complex diseases imply the possible roles of gene-by-obesity or gene-by-lifestyle interactions on the risk of dyslipidemia or hypertension. Current genetic studies, including genome-wide association studies (GWASs), have identified more than 500 and 800 variants of lipids and blood pressure (BP) levels, respectively. Even though recent GWASs have successfully identified dozens of genetic markers related to plasma lipids or BP levels, the interaction structures are not well-known. Thus, we intended to search lipid-associated or BP-associated variants modifying the effect of lifestyle factors, such as cigarette smoking, alcohol consumption, and obesity, on the risk of dyslipidemia or hypertension at a genome-wide scale.

Materials and Methods: A total of 18,025 individuals of Korean descent from four independent genome cohorts, a part of the Korean Genome and Epidemiology Study (KoGES), were included in this study. We determined dyslipidemia and hypertension by using the clinical cut-offs of high-risk CVD groups; lifestyle factors in this study were also defined based on the clinical thresholds. We conducted emerging analytical

models as possible to investigate gene-by-obesity and gene-by-lifestyle interactions on the risk of dyslipidemia and hypertension for Koreans; a total of 3,914,038 single-nucleotide polymorphisms (SNPs) were examined for detecting GxEs. We replicated all the findings by using the independent Korean genome cohorts and estimated how much phenotypic variance or heritability was additionally explained by considering gene-by-obesity or gene-by-lifestyle interactions. These two independent studies on dyslipidemia and hypertension were further investigated by using the different scales of outcomes (continuous vs. dichotomous) to estimate whether the scale differences had affected the results from our previous genome-wide interaction scans (GWISs).

Results: In GWISs for dyslipidemia, we identified and replicated about 20 gene-by-obesity interactions attributable to novel genetic variants (*SCN1A* and *SLC12A8*) and lipid-associated variants (*APOA5*, *BUD13*, *ZNF259*, and *HMGCR*), which have been reported in previous studies. Genetic contributions, on the other hand, were markedly higher when several independent gene-by-obesity interactive SNPs were present for each pair of lipids and environmental factors. The gain of heritability was substantial for triglycerides (TGs) but mild for low-density lipoprotein cholesterol (LDL-C) and total cholesterol (Total-C); GxEs explained up to 18.7% of TG, 2.4% of LDL-C, and 1.9% of Total-C heritability with waist-hip ratio (WHR). In GWISs for hypertension, we newly found and replicated 24 gene-by-lifestyle interactions attributable to novel variants (*BRAP* and *SH2B3*), BP-associated variants (*ATP2B1*), and genetic variants associated with alcohol consumption (*ALDH2*, *CUX2*, *HECTD4* (*C12orf51*), *MYL2*, *OAS3*) and obesity (*ST5*). Genetic contributions increased with differences between GWAS-identified and total genetic impacts of 0.3-2.1% by considering the combined

effect of marginal genetic associations and interactions of the identified variants with lifestyle factors. In quantitative GWISs for lipids and BP levels, moreover, we found and replicated four genetic markers located on *APOA5* and *BUD13*, which interacted with obesity and modified TG levels. All the findings were in linkage disequilibrium (LD) with rs1558860 located on *BUD13*, which reported in our previous GWISs for the risk of abnormal TG elevation, except for rs2041967 ($r2$=0.20). We also found a novel SNP located on *TSPAN5* interacting with heavy drinking to modify SBP levels.

Conclusions: Our findings suggest that some individuals are prone to develop lipid abnormalities or hypertension, even though they are categorized into normal or even into the low-risk group based on lifestyle factors, such as cigarette smoking, alcohol consumption, and obesity traits. Moreover, the ethnic diversities in the risk alleles of lipid or BP indices might explain the differential risk of dyslipidemia or hypertension between populations. These newly identified gene-by-obesity and gene-by-lifestyle interactions can be used to classify individuals into higher-risk or lower-risk groups of each complex trait and to personalize health guidelines for managing lipids or BP levels or lifestyle risk factors according to an individual's genetic constitution.

Keywords: Dyslipidemia; Hypertension; High Blood Pressure; Cigarette Smoking; Alcohol Consumption; Obesity; Gene-by-Environment Interaction (GxE); Genome-Wide Interaction Scan (GWIS); Missing Heritability; Meta-Analysis;

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Contents

Abbreviations

2-*df*, two degrees of freedom test

3-*df*, three degrees of freedom test

AGEN-BP, Asian Genetic Epidemiology Network Blood Pressure

AHA, American Heart Association

ARIC, Atherosclerosis Risk in Communities

BMA, Bayes model averaging method

BMI, body mass index

BP, blood pressure

CC, case-control test (standard test for interaction terms)

CHARGE, Cohorts for Heart and Aging Research in Genome Epidemiology

CNV, copy number variation

CO, case-only test

CT1, cocktail I approach

CT2, cocktail II approach

CVD, cardiovascular disease

DBP, diastolic blood pressure

DG, disease-gene association test

DG1, DG in step-1 and EB in step-2

DG2, DG in step-1 and CC in step-2

DNA, deoxyribonucleic acid

EB, empirical Bayesian test

EDGxE, EG+DG in step-1 and CC in step-2

EG, environment-gene correlation test

EG2, EG in step-1 and CC in step-2

FHS, Framingham Heart Study

GBD, global burden of disease

GENOA, Genetic Epidemiology Network of Arteriopathy

Global BPgen, Global Blood Pressure Genetics

GRS, genetic risk score

GWAS, genome-wide association study

GWIS, genome-wide interaction scan

GxE, gene-by-environment interaction

GxG, gene-by-gene interaction

h^2, narrow-sense heritability

H^2, broad-sense heritability

H2, hybrid method

HBP, high blood pressure

HBP-S1, hypertension stage 1

HBP-S2, hypertension stage 2

HC, hip circumference

HDL-C, high-density lipoprotein cholesterol

HyperGEN, Hypertension Genetic Epidemiology Network

IRB, Institutional Review Board

KNHANES, Korean National Health and Nutrition Examination Survey

KoGES, Korean Genome and Epidemiology Study

KOSIS, Korean Statistical Information Service

KSSO, Korean Society for the Study of Obesity

LD, linkage disequilibrium

LDL-C, low-density lipoprotein cholesterol

MAF, minor allele frequency

MAP, mean arterial pressure

Mid-BP, mid-blood pressure

NCEP, National Cholesterol Education Program

NGS, next-generation sequencing

NIAAA, national institute on alcohol abuse and alcoholism

NIH, National Institutes of Health

OR, odds ratio

OR_D, marginal odds ratio

OR_G, main SNP odds ratio

OR_{GxE}, interactive odds ratio

PP, pulse pressure

Remnant-C, remnant cholesterol

SBP, systolic blood pressure

SHARe, SNP Health Association Resource

SNP, single-nucleotide polymorphism

TG, triglyceride

Total-C, total cholesterol

UKB, United Kingdom Biobank

VIF, variance inflation factor

WC, waist circumference

WES, whole-exome sequencing

WGS, whole-genome sequencing

WHR, waist-hip ratio

List of Tables

List of Figures

List of Supplemental Tables

List of Supplemental Figures

Chapter I.

Introduction

1. Background

1.1. Polygenic Inheritance

Many human traits or diseases are known to be a consequence of the combined effect of genes, environmental factors, and interactions of them. These complex traits, also known as multifactorial or quantitative traits, do not simply follow Mendel's laws of inheritance: the law of 1) uniformity, 2) segregation, and 3) independent assortment. The polygenic model (also termed the infinitesimal model) proposed by R.A. Fisher in 1918 can explain the continuous variation of such traits. It assumes that a variation in complex traits is influenced by several genes having a small effect on phenotypes, as well as by environmental factors. Despite the successful description in inheritance patterns, it remained unclear until the past decade how many genes or genetic factors would actually be significant for driving human complex traits or diseases.

1.2. Genome-Wide Association Study

A genome-wide association study (GWAS) is an approach for testing associations of genetic markers, called single-nucleotide polymorphisms (SNPs), with specific traits in the entire genome (1-3). The first GWAS using early versions of high-density SNP chips was reported in the early 2000s (4, 5). During the past ten years, GWASs have

led to many remarkable findings of human complex traits (6, 7); the GWAS Catalog, an online database compiling the results of GWASs, contains 7,796 publications and 159,202 SNP-trait associations in October of 2019. The advent of GWASs and more lately next-generation sequencing (NGS) technologies, such as whole-exome (WES) and whole-genome sequencing (WGS), has provided opportunities to understand the genetic basis of human complex traits or diseases in detail.

1.3. Missing Heritability

Heritability, the ratio of genetic components to total phenotypic variance, is a major population parameter measuring the contribution of genetic factors to complex traits (8). It is formally defined as the proportion of total phenotypic variation attributable to additive or total genetic variances: the narrow-sense heritability (h^2) or the broad-sense heritability (H^2), respectively (8, 9). Despite success in the findings of dozens of SNPs associated with complex traits, a substantial amount of heritability remains unclear; the identified SNPs only explain a fraction of the predicted heritability. This mystery has been termed the missing heritability (10, 11).

There are several explanations and potential sources of the missing heritability: 1) a number of variants having moderate or smaller effects than GWAS-identified SNPs, 2) genetic variants of low minor allele frequency (MAF) or rare variants 3) gene-by-gene interactions (GxGs), 4) structural or copy number variations (CNVs) including insertions and deletions, and 5) epigenetic alterations, such as deoxyribonucleic acid (DNA) methylations and histone modifications (10-13). Interactions between genes

and environmental factors are also suggested to be the potential source of the missing heritability (12, 13).

2. Gene-by-Environment Interaction

2.1. Definition

In epidemiology, the term interaction is used to describe a phenomenon in which two or more factors change the other's effect on a given outcome; it is also known as the effect modification. An interaction occurs when 1) the first factor's effect on a given outcome is not homogeneous in subgroups stratified by the second risk factor, and 2) the observed joint effect of the factors differs from the expected joint effect based on their independent effects. Similarly, the term gene-by-environment interaction (GxE) is broadly defined as the joint effect of genes with environmental factors that are not explained by their marginal effects separately (14, 15).

2.2. Genome-Wide Interaction Scan

Current GxE studies have applied a candidate-gene approach to detect the interaction of genes with environmental factors. They have focused on a candidate region, which was localized based on prior information, usually consulted from GWASs estimating effects on marginal genetic associations. Candidate GxE studies tend to provide more power for testing interactions if the assumption about candidate-genes is appropriate; these studies, however, are incapable of finding novel genes independent from prior

information (16). A genome-wide interaction scan (GWIS), by contrast, investigates the entire genome to find interactions of genetic loci with weak or moderate marginal genetic effects as well as strong marginal effects. GWISs can pinpoint genes without any prior information; studies using the entire genome, such as GWISs and GWASs, are labeled as hypothesis-free or hypothesis-generating methods (17, 18). Genome-wide approaches, however, have low statistical power due to the number of analyses performed independently (19, 20). GWISs focus on the estimate of effect differences between subgroups stratified by each gene and environmental factor, not the genetic effects on marginal associations mainly estimated in GWASs.

2.3. Reasons and New Opportunities

There are many incentives to investigate the interaction structure between genes and environmental factors: 1) providing insights into the biology of human complex traits or diseases, 2) developing better prognostic or prediction models to manage diseases, 3) detecting high-risk groups in a given population and providing personalized health guidelines for them, and 4) allowing new opportunities for prevention and treatment of diseases (21-23). Moreover, the missing heritability may be explained additionally by the modifying effects of genetic factors attributable to GxEs.

With available high-volume genetic data, such as NGS and multi-omics data, a study of GxEs has been a focus of genetic and epidemiological researches for several years. There are several successful findings from researches on GxEs: especially studies of metabolism genes and pathways, functional approaches, and model systems (21-24).

There are ongoing discussions about the incorporation of biological knowledge into the emerging GxE analyses; the use of gene-based, pathway-based, and multi-omics approaches may result in the identification of novel disease susceptibility loci, which contribute to the heritability (15, 24).

2.4. Current Challenges

Even though these successful studies have motivated researchers to find and describe how the interplay between genes and environmental factors influences complex traits or diseases, most of the studies have focused on only a few candidate-genes. Only a few studies on GxEs have been conducted to scan the entire genome to detect genetic loci interacting with environmental factors. It is mainly attributable to the limitations of GxE testing: 1) the inherently low statistical power, 2) the complexity of assessing environmental factors, 3) measurement errors, 4) restricted variations in both genetic and environmental factors, 5) the scale dependence in definition of interactions, and 6) the lack of functional data on genetic variants (22, 25-29). On the other hand, new approaches, study designs, and statistical methods have been suggested to overcome these limitations and facilitated GxE analyses using the entire genome (30, 31).

3. Dyslipidemia

3.1. Clinical Definition

Dyslipidemia indicates an abnormal state of one or more lipid levels in the blood. It

is usually determined by using the following lipid profiles: elevated total cholesterol (Total-C) or low-density lipoprotein (LDL-C) or triglyceride (TG) or reduced high-density lipoprotein cholesterol (HDL-C). Clinical cut-off points of each lipid profile, suggested by the National Cholesterol Education Program (NCEP), for dyslipidemia are as follows (32): 1) Total-C over 6.21 mmol/L or 2) HDL-C less than 1.03 mmol/L for males or less than 1.29 mmol/L for females or 3) LDL-C over 4.14 mmol/L or 4) TG over 2.26 mmol/L (Supplemental Table S1).

3.2. Epidemiological Studies

Dyslipidemia is a well-established risk factor for cardiovascular disease (CVD); the associations between lipid abnormalities and CVD risk are supported robustly by the accumulated findings from large-scale epidemiological studies (33-37). Even though there is an ongoing debate over the causative role for HDL-C in the risk of CVD (38), abnormalities in plasma levels of HDL-C and Total-C remain unimpeachable clinical predictors in the assessment of CVD risk (33, 36, 39, 40). Lowering LDL-C by using lipid-lowering drugs, such as statins, on the other hand, has become a key treatment for primary prevention of CVD in the last few decades (37, 41). TG-rich lipoproteins and their remnants have been reported as contributors to the remaining CVD risk in recent Mendelian randomization studies (34, 35, 42-44).

3.3. Genetic Studies

Blood lipids are known to be heritable and modifiable (45, 46); many genetic studies and meta-analyses have been performed to find out lipid-associated genes to develop

new therapies for CVD management and prevention (47-51). GWASs have identified more than 500 loci influencing plasma lipid levels in European ancestry cohorts (52-62). The total variance explained by these loci in the Framingham Heart Study (FHS) was about 15.0% for quantitative Total-C levels, 13.7% for HDL-C levels, 14.6% for LDL-C levels, and 11.7% for TG levels, corresponding to 25-30% of the heritability of each lipid trait (52-54).

3.4. Gene-by-Obesity Interaction Studies

Previous GWASs on lipid profiles have been successful in terms of both the richness of robustly replicated loci and the genetic variances explained by these variants, but the current list of loci in the GWAS Catalog is based on marginal association models assuming a lack of genetic interactions, such as GxEs and GxGs. However, the ethnic differences in abnormal lipid profiles reactive to obesity suggest that the interaction between genetic background and obesity traits may play a specific role in regulating lipid concentrations (63). Compared with non-Hispanic whites, for example, African Americans have a lower prevalence of dyslipidemia despite a higher obesity risk (63, 64). Conversely, despite similar or leaner body compositions than Caucasians of the same age and sex, the prevalence of dyslipidemia is increased in Asians (63, 65, 66), particularly those of Korean descent (63, 67, 68).

A growing body of evidence from candidate-gene studies also supports the presence of gene-by-obesity interactions in lipid abnormalities; the effects of lipid-associated loci are modified according to obesity indices, such as body mass index (BMI), waist

circumference (WC), and waist-hip ratio (WHR) (69-73). Only a few studies, on the other hand, have been performed at a genome-wide scale to identify genetic variants influencing lipid levels based on obesity status. Moreover, these studies were carried out using a genetic risk score (GRS) or a two-step approach rather than an exhaustive method (74-77). Current findings of gene-by-obesity interactions on abnormal lipid profiles are also predominantly based on Europeans (69-71, 73-77); the GxE effects could have been underestimated if non-Caucasians are more susceptible to genes of dyslipidemia reactive to obesity.

4. Hypertension

4.1. Clinical Definition

Hypertension, also known as high blood pressure (HBP), is a chronic condition with a persistent abnormal elevation of the blood pressure (BP) in the arteries. It is usually determined by elevated levels of systolic BP (SBP) or diastolic BP (DBP). Recently, the American Heart Association (AHA) has suggested two stages of hypertension in their guidelines for prevention, detection, evaluation, and management of HBP (78): stage 1 (HBP-S1; 130≤SBP<140 mmHg or 80≤DBP<90 mmHg) and stage 2 (HBP-S2; SBP≥140 mmHg or DBP≥90 mmHg) (Supplemental Table S1).

4.2. Epidemiological Studies

Hypertension, also referred to as HBP, is the most common and modifiable risk factor

for CVD, mortality, and disability around the world (79). Even within normal ranges, elevated levels of SBP or DBP have a graded and continuous influence on CVD risk (80). Increased SBP has been reported to be associated with the highest global burden of disease (GBD) among risk factors in 2015. It is even higher than the global burden of cigarette smoking or obesity (79); GBD attributable to HBP has been described in detail for 2005, 2010, and 2015 (79, 81, 82). Moreover, the benefit of reducing levels of BP for management of CVD has already been proven in clinical trials, large-scale epidemiological studies, meta-analyses, and systematic reviews (83).

The mortality attributable to CVD is remarkably decreasing in the United States and Canada (84, 85); mortality due to CVD for Koreans, on the other hand, has continued to increase according to the Korean Statistical Information Service (KOSIS). These trends in CVD-related mortality seem to depend on whether major CVD risk factors, such as hypertension and dyslipidemia, are well controlled or not (85, 86). The recent decrease in CVD-related mortality in Western countries, for example, is mainly due to the declining prevalence of CVD risk factors (85). The prevalence of hypertension and dyslipidemia among middle-aged Koreans, by contrast, has been even increasing or remaining constant (87); hypertension is the most prevalent (25.8%) health-related condition, followed by dyslipidemia (16.6%) (88).

4.3. Genetic Studies

Evidence from genetic studies, such as GWASs, exome-wide association studies, and meta-analyses in various ethnic groups, has found several genetic variants associated

with quantitative BP and hypertension (89-93). In 2009, 13 independent genetic loci associated with BP and HBP were reported from two European consortia: the Global Blood Pressure Genetics (Global BPgen) and Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) (89, 90). On the other hand, the Asian Genetic Epidemiology Network Blood Pressure (AGEN-BP) group newly reported five loci associated with SBP and DBP among East Asian ancestry groups (92).

Recent GWASs have identified more than 800 loci associated with BP traits, such as SBP, DBP, and pulse pressure (PP), among one million people of European ancestry drawn from the United Kingdom Biobank (UKB) (94, 95). The heritability of BP is moderate; it is about 40% across twin and family-based studies (96). The heritability attributable to common (MAF>0.10) variants for SBP and DBP in European ancestry is 20% and 27%, respectively. For African ancestry, on the other hand, the heritability due to common SNPs for SBP and DBP is 50% and 39%; the estimates are based on data from the Atherosclerosis Risk in Communities (ARIC) population-based cohort study (97). Only a small fraction, less than 5%, of the total variance is attributable to GWAS-identified BP SNPs (98).

4.4. Gene-by-Lifestyle Interaction Studies

Several GxE studies have already been proposed to elucidate the genetic architecture of hypertension (99-104). Two novel BP loci interacting with cigarette smoking have been found in African American individuals, according to the Hypertension Genetic Epidemiology Network (HyperGEN) study and the Genetic Epidemiology Network

of Arteriopathy (GENOA) study (103). Seven significant and 21 suggestive BP SNPs, including genetic variants interacting with cigarette smoking, have been found from the FHS SNP Health Association Resource (SHARe) (101); they have also identified one significant and 20 suggestive BP loci interacting with alcohol consumption (100). Chinese research on BP, on the other hand, has reported ten lipid-associated variants interacting with overweight or obesity to modify effects on BP (99). However, most results from these GxE studies on BP are based on candidate-gene or two degrees of freedom (2-*df*) tests. There are relatively fewer GxE studies on HBP, focusing on the interplay between genes and lifestyle factors at a genome-wide set of variants.

5. Aims of the Thesis

The main purpose of this thesis is to identify the interaction of genetic susceptibility loci with modifiable environmental factors and suggest the general framework to test the interactions at a genome-wide scale. We investigated genetic markers interacting with lifestyle factors to modify the risk of dyslipidemia and hypertension, estimated additional heritability attributable to the variants, and compared results between GxE analyses using dichotomous and quantitative outcomes. For this end, we carried out two independent studies applied emerging statistical methods for testing GxE in the entire genome: 1) a genome-wide search for gene-by-obesity interactions on the risk of dyslipidemia and 2) a genome-wide search for genetic interactions with cigarette smoking, alcohol consumption, and obesity, so-called lifestyle factors, on the risk of hypertension. These two independent studies were also further investigated by using

a quantitative scale of the phenotypes: 3) a genome-wide search for gene-by-lifestyle interactions on quantitative lipid and BP levels.

In the first study, we hypothesized that some genetic variants modified the effects of obesity on the risk of dyslipidemia and assumed that these genetic loci might include both novel and known genes with different reactive effect sizes. We also proposed a hypothesis that the novel gene-by-obesity interactions underlying lipid traits explain more of the total and genetic variances of each lipid parameter than do the SNPs with only marginal effects. In the second study, we investigated the interactions of genetic markers with lifestyle factors, such as cigarette smoking, alcohol consumption, and obesity, on the risk of hypertension. We also proposed a hypothesis that the total and genetic variances of HBP are additionally explained by the newly detected gene-by-lifestyle interactions underlying HBP parameters. In the third study, we hypothesized that there was some novel and known genes modifying the effects of lifestyle factors on quantitative lipid and BP levels. We also expected that the identified variants were replicated with our previous findings and had consistent directions of genetic effects regardless of the scale of outcome variables.

In general, a genome-wide analysis for testing GxEs is believed to suffer from weak statistical power rather than type 1 errors or false-positive findings (105). Partly due to this issue, replicating new findings has not been widely accepted as a prerequisite for reporting GxEs. However, we believe replications in GxE studies are as important as in GWASs. For identifying and replicating gene-by-obesity and gene-by-lifestyle

interactions at a genome-wide scale, we carried out emerging GxE methods by using four independent Korean genome cohorts. The identification of genetic interactions with potentially modifiable risk factors will facilitate the knowledge-based approach to personalize health-related guidelines according to an individual's genetic profile.

Chapter II.

Review of Analytical Methods for Gene-by-Environment Interactions

1. Background

1.1. Low Statistical Power

As outlined previously, low statistical power is the inherent limitation of GxE studies on complex traits or diseases (22). Compared with a GWAS focusing on the marginal or direct association test, the analysis on GxEs requires much larger sample sizes to find interactions between genes and environmental factors. Furthermore, the sample size requirement is further inflated to overcome the problem of multiple comparisons for testing interactions at a genome-wide scale (15, 105). Therefore, most analytical methods have emerged to improve the power of testing GxEs (30, 31).

Each analytical GxE model, on the other hand, provides differential statistical power of detecting interactions between genes and environmental factors, mainly according to marginal genetic and GxE effects (30). If we have any prior information about the effect sizes, we will choose a specific test offering substantially greater power to test GxEs at a genome-wide scale. Unfortunately, it is hard to know any prior information about the marginal and interactive effects of each locus. As type 1 error rates or false-positive findings are generally considered to be less problematic than underpowered

findings, it is recommended to use multiple analytical GxE models as possible (105). Further verification can be done by replications or stratified analyses for a candidate region localized by previous GxE analyses.

1.2. Overview of Exhaustive Scans

There are several analytical methods for testing interactions at a genome-wide scale: ten different approaches for this GWIS (30). GWISs can be classified into two main test types: 1) an exhaustive scan and 2) a two-step method, including screening (step-1) and hypothesis testing (step-2). Exhaustive scans, such as case-control (CC), case-only (CO) (106), and empirical Bayesian (EB) approaches (107), are direct one-step methods. A CC approach, for example, tests an interaction term of a standard logistic regression model; it estimates the effect differences between subgroups stratified by each genetic and environmental factor (30). A CO approach estimates environment-gene correlation (EG) in the affected individuals; it provides greater statistical power than a CC method if genetic and environmental factors are independent in the source population (106, 108). An EB method integrates the results from a CC test with those of a CO test; it also provides greater statistical power than a CC approach (107, 109).

1.3. Overview of Two-Step Methods

Two-step methods, on the other hand, consist of a screening (step-1) and hypothesis testing (step-2). All the two-step approaches require a disease-gene association (DG) or EG information in step-1 to screen candidate SNPs interacting with environmental factors (30). There are various two-step approaches to identify GxE loci: 1) screening

with DG and testing with EB (DG1), 2) DG in step-1 and CC in step-2 (DG2) (110), 3) EG in step-1 and CC in step-2 (EG2) (111), 4) a hybrid (H2) test (105), 5) Cocktail I (CT1), 6) Cocktail II (CT2) (112), and 7) combining both DG and EG in step-1 and CC in step-2 (EDGxE) (30). H2, CT1, CT2, and EDGxE methods require the results from DG and EG tests to screen candidate loci in step-1; a H2 test uses these tests in parallel, CT1 and CT2 tests adopt the information flexibly depending on the *p*-values of each DG and EG test, and an EDGxE method combines the results of DG and EG tests to generate new screening statistics. For step-2, H2 and EDGxE methods reflect the results of CC tests; CT1 and CT2 methods use an EB test if step-1 is based on a DG test and adopt a CC test if an EG test is used for a screening step (30). Analytical approaches, such as exhaustive scans and two-step methods, could be categorized by 1) the assumption of independence between genetic and environmental factors in the source population, 2) methods for screening (step-1), and 3) methods for hypothesis testing (step-2) (Supplemental Figure S1).

2. Exhaustive Scans

2.1. Case-Control Analysis

In a CC study consisting of N participants, we define D_i (i=1, 2, ..., N) as an indicator of disease and E_i (i=1, 2, ..., N) as an environmental factor. Each SNP will be denoted G_i (i=1, 2, ..., N), which are usually coded as 0, 1, or 2 for genotype AA (two common alleles), Aa (one common allele and one minor allele), or aa (two minor alleles). For a GWAS, the marginal genetic effect on disease is estimated by the genetic odds ratio

(OR_G), which can be obtained as the exponential of λ_G from the following statistical model: $\text{logit}(\Pr(D_i=1|G_i))=\lambda_0+\lambda_G G_i$. This logistic regression model can be augmented to test GxEs: $\text{logit}(\Pr(D_i=1|G_i))=\beta_0+\beta_G G_i+\beta_E E_i+\beta_{GxE} G_i x E_i$. In this equation, the GxE effect on disease status is measured by the interactive odds ratio (OR_{GxE}), which can be obtained as the exponential of β_{GxE} from the augmented logistic regression model. We denote the approach using the augmented model as the CC analysis (30).

2.2. Case-Only Analysis

A standard CC analysis generally has low statistical power of detecting GxEs; a CO analysis can provide substantially greater power if genetic and environmental factors are independent in the source population (106, 108). A CO method estimates EG, the correlation between environmental factors and each SNP, in the affected individuals. The GxE effect on disease status is consistently estimated by the odds ratio (OR) for the genetic term, which can be obtained as the exponential of γ_{GxE} from the following logistic regression model: $\text{logit}(\Pr(E_i=1|G_i,D_i=1))=\gamma_0+\gamma_{GxE} G_i$. We denote the analysis using this equation as the CO analysis (30, 106, 108).

2.3. Bayesian Approach

Even though a CO analysis provides substantially greater power than a standard CC analysis, type 1 errors or false-positive rates of a CO test can be inflated unacceptably if the baseline assumption of independence between genes and environmental factors is violated (30, 106, 108). Bayesian approaches, such as an EB analysis and a Bayes model averaging (BMA) method (107, 109), have emerged to provide enough power

of testing GxEs without the potential inflation of type 1 errors or false-positive rates (30). EB and BMA methods integrate the estimated GxE effects from a CC test with those of a CO test; these Bayesian approaches reflect a measure of uncertainty about the baseline assumption of independence between genetic and environmental factors (107, 109, 113). Although EB and BMA methods can improve power to detect GxEs, these analyses can also induce type 1 errors or false-positive findings in the presence of correlation between genetic and environmental factors (105, 114).

3. Two-Step Methods

3.1. Hybrid Method

Two-step approaches have suggested providing substantial power of detecting GxEs while preserving acceptable type 1 errors or false-positive rates (105, 110, 111). Any of the two-step methods require independence between screening (step-1) and testing (step-2) statistics (115). DG1 and DG2 tests use statistics for the marginal association of each variant to screen candidate SNPs in step-1. They conduct an EB or a CC test in step-2, respectively; the number of candidate SNPs screened in step-1 is reflected in Bonferroni correction (110). A DG1 method is known to be more powerful than a DG2 method (112). DG1 and DG2 methods satisfy the assumption of independence between screening and hypothesis testing statistics.

An EG2 approach, on the other hand, defined screening statistics as S_{EG}, the statistics

from EG correlation tests of each variant. The following logistic regression model is used to test the EG correlation: $\text{logit}(\Pr(E_i=1|G_i))=\delta_0+\delta_G G_i$. For an EG2 approach, a CC analysis is conducted for hypothesis testing in step-2; the significant level is also adjusted for Bonferroni correction (111). A H2 methods uses S_{DG} and S_{EG} in parallel for screening candidate SNPs in step-1 and tests GxEs of each SNP in step-2 by using a standard CC test; the number of combined SNPs passed DG or EG screening steps is reflected in Bonferroni correction (105).

3.2. Cocktail Approach

CT1 and CT2 approaches also use the DG and EG results in parallel. A CT1 approach adopts different statistics for screening in step-1, according to the estimated *p*-values: 1) $S_{CT}=S_{DG}$ if the *p*-value of S_{DG} is less than a given threshold, usually 0.001, and 2) $S_{CT}=S_{EG}$ otherwise. A CT2 approach, on the other hand, defines S_{CT} as the maximum value of S_{DG} and S_{EG}: 1) $S_{CT}=S_{DG}$ if the *p*-value of S_{DG} is less than the *p*-value of S_{EG} and 2) $S_{CT}=S_{EG}$ if the *p*-value of S_{EG} is less than the *p*-value of S_{DG}. For the hypothesis testing in step-2, both cocktail methods use S_{EB} if $S_{CT}=S_{DG}$ and S_{CC} if $S_{CT}=S_{EG}$ (112).

3.3. EDGxE Method

The emerging two-step methods, such as DG1, DG2, EG2, and cocktail approaches, use both DG and EG information for screening candidate SNPs in step-1; the use of both S_{DG} and S_{EG} enhances the statistical power of detecting GxEs at a genome-wide scale (30, 110, 111). These two-step methods, however, do not consider S_{DG} and S_{EG} simultaneously; we need to select one or the other statistic of a given SNP in step-1.

An EDGxE method differs from the previous two-step methods in that this approach simultaneously considers both S_{DG} and S_{EG} to prioritize SNPs for hypothesis testing; it defines screening statistics, S_{EDGxE}, as the sum of S_{DG} and S_{EG}. An EDGxE method adopts GxE statistics, S_{CC}, estimated by using a standard CC analysis for hypothesis testing in step-2 (30); the screening (step-1) and hypothesis testing (step-2) statistics are also independent of each other.

4. Type 1 Error and Statistical Power

4.1. Type 1 Error

The suggested analytical models for testing GxEs, such as CC, CO, EB, and several two-step methods, achieved permissible type 1 error rates around the nominal alpha of 0.05 in simulation studies with multiple scenarios (30, 116). In simulation studies with 3,500 cases and 3,500 controls, so-called CC settings, false-positive rates were estimated by varying the number of disease susceptibility loci with DG associations or EG correlations (Reference Table R1). Exhaustive tests using CC and EB, and all two-step approaches, as expected, achieved the nominal type 1 error or false-positive rates regardless of the presence of SNPs with DG associations or EG correlations in the source population. CO analyses, by contrast, had extremely high (>0.999) false-positive rates if any variants had EG correlations in the source population (30). These trends of type 1 error rates were constant in population settings with 1,000 cases and 1,000 to 9,000 controls (116). The independence between genes and exposures need to be considered to avoid possible false-positive findings from CO analyses.

4.2. Statistical Power

The emerging analytical approaches, on the other hand, show a differential power to test GxEs in simulation studies with multiple scenarios (30, 116). In the CC settings, statistical power was investigated by varying the magnitude of marginal associations and interactions, the frequency of genetic and environmental factors, and the number of SNPs having DG or EG correlations (Reference Table R2 and Figure R1). If there are no significant EG correlations in the source population, the CO analysis provides substantially greater power of testing GxEs than the standard CC analysis (106, 108). The EDGxE method considering both S_{DG} and S_{EG} to prioritize SNPs for hypothesis testing provides the highest power than the other approaches in most scenarios (30).

In the population settings, on the other hand, the true-positive rate or statistical power was simulated by varying the prevalence of disease and exposure, and the magnitude of interactions (Reference Figure R2) (116). Similar to the assessed power in the CC settings, the CO test provides higher power to detect GxEs than the other exhaustive scans, such as CC and EB, regardless of the prevalence of disease and exposure, and the OR_{GxE}. Two-step approaches, on the other hand, show substantially greater true-positive rates than exhaustive scans. In most scenarios, the H2 achieves a higher true-positive rate; the modified H2 method (116, 117), which considers both S_{DG} and S_{EG} in the screening step as like as the EDGxE, offers the highest power. In general, it is recommended to use multiple analytical models as possible to test interactions (105), because it is hard to have any prior information about marginal associations or GxEs at genome-wide scales. We can further verify the findings by replications or stratified analyses for a candidate region localized by previous GxE studies.

Chapter III.

A Genome-Wide Search for Gene-by-Obesity Interaction Loci of Dyslipidemia

1. Materials and Methods

1.1. Participants

A total of 18,025 individuals from four independent Korean cohorts with a genome-wide set of SNPs were included in this study on dyslipidemia: 4,637 individuals from the Ansan cohort, 4,205 individuals from the Ansung cohort, 3,700 individuals from the urban cohort, and 5,483 individuals from the rural cohort. Participants who have suffered cancer or diabetes were excluded from this study; people taking any kind of lipid-lowering drug were considered as dyslipidemia patients (Supplemental Figure S2). Table 1 shows the baseline characteristics of each Korean cohort (Supplemental Table S2 and S3); a total of 16,014 individuals were included in this study.

Participants in the reference set, the Ansan and Ansung cohorts, were aged about 40-69 years and recruited from industrialized suburban and rural regions of the Republic of Korea. Participants in the replication set, including the urban and rural cohorts, on the other hand, were aged over 40 years and recruited from urban medical institutions and rural areas of Korea: Gangwha, Goryeong, Namwon, Pyeongchang, Wonju, and Yangpyeong. These cohorts are part of the Korean Genome and Epidemiology Study

(KoGES), an ongoing population-based cohort study initiated in 2001 to understand chronic diseases among Koreans. The research protocols and data in this study were approved by the Institutional Review Board (IRB) of Seoul National University (IRB number: E1805-003-001) and followed the Declaration of Helsinki principles.

1.2. Measurements

Data on health status, health-related behaviors, and medical and medication histories were collected through a standardized questionnaire. Trained experts at each clinical center conducted anthropometric measurements, specimen collection, and laboratory tests. All participants provided informed consent for the baseline data and specimens; more detailed protocols were described in previous reports (118, 119). Total-C, HDL-C, and TG were measured using traditional enzymatic methods in the blood samples drawn after an 8-hour fast. For individuals with TG under 4.52 mmol/L, LDL-C was calculated using the Friedewald's formula (120); we determined remnant cholesterol (Remnant-C) as the level of Total-C minus HDL-C minus LDL-C (42, 44). We used directly measured height, weight, WC, and hip circumference (HC) to calculate BMI and WHR, the obesity traits.

1.3. Phenotypes

We defined dyslipidemia based on clinical cut-offs of high-risk CVD groups reported in the NCEP guides (32): 1) Total-C over 6.21 mmol/L, 2) LDL-C over 4.14 mmol/L, 3) TG over 2.26 mmol/L, 4) the lowest quintile of HDL-C, and 5) the highest quintile of Remnant-C. Individuals who have taken any kind of lipid-lowering drug, such as

statins, were considered as dyslipidemia patients in statistical analyses. Obesity traits were defined by using clinical cut-offs suggested by the National Institutes of Health (NIH) and the Korean Society for the Study of Obesity (KSSO) (121, 122). We used a total of six obesity indices: 1) overweight class 1 (BMI≥23.0 kg/m^2), 2) overweight class 2 (BMI≥25.0 kg/m^2), 3) obesity (BMI≥30.0 kg/m^2), 4) abdominal obesity class 1 (WC>90 cm for males, 80 cm for females), 5) abdominal obesity class 2 (WC>102 cm for males, 88 cm for females), and 6) abdominal obesity defined as a WHR above 0.90 for males and 0.85 for females (Supplemental Table S1).

1.4. Genotype Information

We used a genome-wide set of variants genotyped by using the following dense SNP microarrays: the Affymetrix Genome-Wide Human SNP Array 5.0 for the Ansan and Ansung cohorts, the Affymetrix Genome-Wide Human SNP Array 6.0 for the urban cohort and a part of the rural cohort (n=1,816), and the Illumina HumanOmni1-Quad BeadChip for the rest part of the rural cohort (n=3,667). Any variant violating Hardy-Weinberg equilibrium (p-value<$1x10^{-6}$), with genotype call rates below 95%, or with MAF values below 0.01 were excluded. After quality control, the remaining markers were imputed by using the 1000 Genomes Project's haplotypes phase I in NCBI build 37 (GRCh37/hg19) of the Asian references. We used SHAPEIT2 and IMPUTE2 for the haplotype phasing and imputation processes, respectively (123, 124). Only SNPs with quality scores higher than 0.6 were retained, yielding 4,780,608 variants for the reference set and 5,729,661 variants for the replication set. After comparing each set, a total of 3,914,038 overlapping variants were selected as the final genetic markers.

1.5. Statistical Analyses

The risk of dyslipidemia was adjusted for age, age^2, sex, and each obesity trait, such as obesity and abdominal obesity, one by one; the logarithm of OR was corrected by using a logit model. Before GWISs, we conducted marginal DG and EG tests for the 3.9 million SNPs; genetic markers associated with both lipids and obesity traits were excluded to reduce potential pleiotropy (p-value<$1x10^{-3}$). Exhaustive scans, such as CC, CO (106), and EB methods (107), are direct one-step approaches; a CC analysis tests the null hypothesis β_{GxE}=0 using a standard GxE model, a CO analysis tests the EG in affected individuals, and an EB analysis integrates the estimated effects from a CC test with those of a CO test.

Two-step methods, on the other hand, comprise screening and hypothesis testing. We carried out emerging two-step methods in parallel: DG1, DG2 (110), EG2 (111), H2 (105), CT1, CT2 (112), and EDGxE methods (30). H2, CT1, CT2, and EDGxE adopt both DG and EG information to screen genetic markers in step-1; H2 uses these tests in parallel, CT1 and CT2 apply the information flexibly depending on the p-value of DG and EG tests, and an EDGxE combines statistics of DG and EG to generate new screening statistics. For hypothesis testing in step-2, H2 and EDGxE adopt the results from a CC test; CT1 and CT2 apply an EB when screening is based on a DG test and adopt a CC if they use an EG to screen genetic markers.

After finding novel GxE variants, we applied the standard genome-wide significance level (p-value<$5x10^{-8}$) for exhaustive scans. We determined a threshold of screening

as $1x10^{-4}$ for the first step of DG1, DG2, EG2, and H2 methods; for step-2, the subset of SNPs passing step-1 was tested at a more liberal cut-off point (0.05 divided by the number of screened SNPs) (105). We adopted weighted hypothesis testing in step-2 of CT1, CT2, and EDGxE approaches rather than testing only SNPs passing step-1; stepwise penalties due to the marginal *p*-value were applied for each variant in step-2 (125). We removed one of a pair of the identified variants if linkage disequilibrium (LD) was greater than 0.5, which means a variance inflation factor (VIF) was greater than 2, for informed LD pruning (LD clumping). We identified novel GxE loci using the reference set consisting of the Ansan and Ansung cohorts; all identified GxE loci were reconfirmed using the replication set composed of the urban and rural cohorts. We considered the effect size, magnitude of standard error, *p*-value, and the direction of effect to estimate the final result of meta-analyses. We used PLINK (126), METAL (127), and R in the analyses.

1.6. Methods of Evaluating Impacts

We estimated genetic variances attributable to the genetic susceptibility SNPs using the simplified equation $2p(1-p)[\log(OR)]^2$, where p is MAF of the variant and OR is the estimated OR from the logistic regression model for marginal associations (128). The genetic contribution of each variant was estimated using the simplified equation $2p(1-p)[\log(OR_G)]^2/V_P+2ep[(1-p)+2p(e-1)^2][\log(OR_{GxE})]^2/V_P$. In this equation, V_P is the phenotypic variance, e is the prevalence of an environmental factor, and OR_G or OR_{GxE} are estimated ORs due to main SNP or gene-by-obesity interactions from the logistic regression model for GxEs. We used GenABEL, the R package for genome-wide association analyses (129), to estimate the heritability of dyslipidemia from the

Healthy Twin Study, a family-based cohort study in Korea (Supplemental Table S3.e) (130, 131). GCTA, the analysis tool for genome-wide complex traits (132), was also used to estimate the SNP-based heritability attributable to all genetic markers on the SNP microarray. To transform the estimates of phenotypic variance explained on the observed scale to the estimations on the underlying scale, we assessed the prevalence of dyslipidemia from the Korean National Health and Nutrition Examination Survey (KNHANES) (133); the prevalence of abnormal Total-C, HDL-C, LDL-C, TG, and Remnant-C are 11.9%, 30.6%, 10.1%, 17.7%, and 20.0%, respectively.

2. Results

2.1. Characteristics of the Study Populations

Table 1 shows the baseline characteristics of the participants in each Korean genome cohort. We observed age, sex, obesity-related measurements, and plasma lipid levels adjusted for age, age^2, and sex; all features were stratified into subgroups for obesity traits based on BMI, WC, and WHR (Supplemental Table S2 and S3). We examined the adjusted lipids to assess the trends of lipids in each obesity and abdominal obesity subgroup. As expected, the adjusted plasma lipid levels were significantly worsened as a degree of obesity or abdominal obesity status increased in the combined Korean cohort (Supplemental Figure S3).

2.2. Identification of Gene-by-Obesity Interactive Loci

We identified 55 SNPs showing genome-wide significant GxE effects on the risk of abnormal lipid profiles with at least one of the six obesity traits (Supplemental Table S4). After LD clumping based on genetic contributions of each variant to the risk of dyslipidemia, we detected 20 gene-by-obesity interactions attributable to novel SNPs located on *SCN1A* and *SLC12A8* and to lipid-associated SNPs near *APOA5*, *BUD13*, *ZNF259*, and *HMGCR* which were reported in previous GWASs on lipid traits. Table 2 shows the marginal and gene-by-obesity interactive effects of the newly identified loci on the risk of dyslipidemia; we summarized the novel interactions according to the discriminators of obesity traits, such as BMI, WC, and WHR. We also estimated genomic inflation factors (λ) of each genetic effect, such as marginal, main SNP, and interactive effects, in each logistic regression model for testing DG associations and GxEs (Supplemental Table S5). Figure 1 (Supplemental Table S6) describes the risk of lipid abnormalities for each gene and environmental factor; we estimated the OR as the ratio of the probability of dyslipidemia occurring in each exposed group (G≠0 or E≠0) to the probability in a non-exposed group (G=0 and E=0).

We identified three novel variants interacting with obesity traits to change the risk of abnormal elevation of Total-C: rs2878417, rs7702895, and rs7733436. *COL4A3BP*, in particular, exhibited synergistic effects with BMI and WC on the risk of abnormal Total-C elevation. For the interaction between *HMGCR* and WHR, the marginal odds ratio (OR_D) was 0.81 (95% CI, 0.78-0.84); OR_G and OR_{GxE} were 0.72 (95% CI, 0.68-0.77) and 1.22 (95% CI, 1.13-1.30). As shown in Figure 1.a, the multiplicative effect of abdominal obesity was 1.12 (95% CI, 0.96-1.31) for individuals having two wild-

type alleles at rs7702895 (Supplemental Table S6.a). The effect sizes increased with the number of minor alleles: 1.46 (95% CI, 1.28-1.67) for individuals with one minor allele and 1.57 (95% CI, 1.26-1.95) for homozygous minor alleles, respectively.

SCN1A marked by rs11890028 was detected as a novel locus interacting with obesity to change the risk of abnormal reduction of HDL-C. Although the marginal effect of this variant was negligible (P=4.19x10^{-1}), a noticeable GxE effect (P=2.79x10^{-8}) was observed in an exhaustive CO analysis. The estimated OR_D, OR_G, and OR_{GxE} for the interaction between *SCN1A* and BMI were 0.96 (95% CI, 0.91-1.01), 0.92 (95% CI, 0.87-0.96), and 2.30 (95% CI, 1.98-2.67). As shown in Figure 1.e, the multiplicative effect of obesity for common homozygous was 1.42 (95% CI, 1.22-1.65); the effects were 1.99 (95% CI, 1.57-2.52) or 6.24 (95% CI, 4.03-9.64) for heterozygous or rare homozygous, respectively (Supplemental Table S6.e).

LOC101928271 showed antagonistic effects on the risk of LDL-C abnormalities due to BMI. For the identified gene-by-obesity interaction, the estimated OR_D, OR_G, and OR_{GxE} were 0.75 (95% CI, 0.71-0.78), 0.96 (95% CI, 0.88-1.05), and 0.70 (95% CI, 0.63-0.78), respectively. Figure 1.b (Supplemental Table S6.b), describes the effects of overweight class 1; the effect was 1.00 (95% CI, 0.54-1.82) for rare homozygous genotypes. For common homozygous or heterozygous genotypes, on the other hand, obesity acted as a risk factor for abnormal LDL-C elevation; the multiplicative effect was 1.82 (95% CI, 1.61-2.06) and 1.34 (95% CI, 1.12-1.61), respectively.

We identified six novel SNPs with modifiable effects on the risk of abnormalities in TG due to obesity traits: rs1558860, rs180378, rs2075291, rs651821, rs918144, and rs77008808. *BUD13* and *APOA5* have already been reported as lipid-associated loci, and the marginal effects of these loci on the risk of abnormal TG elevation were also markedly significant in this study. *BUD13* marked by rs918144 showed a risky GxE effect attributable to WC; OR_D, OR_G, and OR_{GxE} were 0.71 (95% CI, 0.69-0.73), 0.66 (95% CI, 0.64-0.70), and 1.17 (95% CI, 1.10-1.24), respectively. As shown in Figure 1.c (Supplemental Table S6.c), the multiplicative effects of abdominal obesity class 1 for common homozygous was 1.56 (95% CI, 1.40-1.76); for heterozygous and rare homozygous, the estimated effects were 1.68 (95% CI, 1.52-1.86) and 2.12 (95% CI, 1.76-2.56), respectively. Conversely, *APOA5* marked by rs651821 showed protective GxE effects due to WHR; OR_D, OR_G, and OR_{GxE} were estimated to be 1.86 (95% CI, 1.80-1.93), 2.26 (95% CI, 2.13-2.41), and 0.74 (95% CI, 0.69-0.79). As illustrated in Figure 1.f (Supplemental Table S6.f), the multiplicative effects of abdominal obesity for each group were as follows: 2.56 (95% CI, 2.20-2.99) for common homozygous, 1.89 (95% CI, 1.68-2.12) for heterozygous, and 1.39 (95% CI, 1.16-1.66) for people with rare homozygous genotypes.

BUD13 and *APOA5*, besides, were associated with the risk of abnormal Remnant-C elevation. *BUD13* interacted with WC to modify the risk of dyslipidemia; OR_D, OR_G, and OR_{GxE} were 0.75 (95% CI, 0.73-0.77), 0.73 (95% CI, 0.71-0.75), and 1.16 (95% CI, 1.10-1.23), respectively. Figure 1.d (Supplemental Table S6.d) shows the effects of abdominal obesity class 2 on the risk of Remnant-C abnormalities: 1.31 (95% CI, 1.17-1.47) for common homozygous, 1.41 (95% CI, 1.28-1.55) for heterozygous, or

1.77 (95% CI, 1.51-2.07) for rare homozygous genotypes. *APOA5*, on the other hand, had an antagonistic effect due to WHR; OR_D, OR_G, and OR_{GxE} were estimated to be 1.82 (95% CI, 1.77-1.88), 1.99 (95% CI, 1.89-2.09), and 0.82 (95% CI, 0.78-0.86), respectively. Figure 1.g (Supplemental Table S6.g) describes the multiplicative effect of abdominal obesity based on WHR; the estimated effects were 2.20 (95% CI, 1.96-2.46) for people with two wild-type alleles at rs651821. The effects decreased as the number of minor alleles increased: 1.85 (95% CI, 1.69-2.03) for heterozygous people and 1.48 (95% CI, 1.28-1.71) for people with rare homozygous genotypes.

We ascertained the detected gene-by-obesity interactions from another point; Figure 2 (Supplemental Table S7) shows the trends of plasma lipid levels due to changes in BMI for each subgroup stratified by the number of risk alleles of the identified GxE markers. In normal weight (18.5 $kg/m^2 \leq BMI < 25.0$ kg/m^2) individuals having no risk alleles (low-risk group), HDL-C levels decreased by 0.032 mmol/L (95% CI, 0.030-0.034 mmol/L) for each unit (1 kg/m^2) increase in BMI; the HDL-C decrement level was 0.039 mmol/L (95% CI, 0.035-0.043 mmol/L) for people having at least one risk allele (high-risk group) and 0.038 mmol/L (95% CI, 0.033-0.043 mmol/L) for upper 50% of people belong to the high-risk group (higher-risk group). The differences in HDL-C decrement levels for each genetic group were more apparent in obese people. For individuals with BMI over 25 kg/m^2, the decrements in HDL-C for the low-risk, high-risk, and higher-risk group were 0.004 mmol/L (95% CI, 0.002-0.006 mmol/L), 0.014 mmol/L (95% CI, 0.010-0.018 mmol/L), and 0.017 mmol/L (95% CI, 0.012-0.022 mmol/L). Similarly, we ascertained that TG increments were different for each genetic group; the increment trends were also more apparent in obese individuals.

2.3. Genetic Contribution of Gene-by-Obesity Interactions

Table 3 presents the genetic contributions due to marginal associations and gene-by-obesity interactions to abnormal lipid profiles. We suggested a proportion of the total heritability for each lipid explained by 1) GWAS-identified SNPs, 2) novel GxE loci, and 3) the combined set of lipid-associated and gene-by-obesity interactive variants, so-called the total genetic impact. The total and SNP-based heritability of the risk of abnormal Total-C elevation was approximately 35.5% and 17.7-24.9%, respectively, after adjusting the risk for age, age^2, and sex. The genetic contributions increased if we considered both marginal genetic associations and gene-by-obesity interactions, with differences between the GWAS-identified and total genetic impact of 1.1-1.9%. The total and SNP-based heritability of the risk of LDL-C abnormalities, on the other hand, was approximately 31.7% and 17.2-25.6%, respectively. For each obesity trait, the total genetic contributions, including interactions, were 0.9-2.4% higher than the marginal genetic impacts due to direct associations only.

The contributions of the combined set of both GWAS-identified and GxE SNPs were markedly higher when several independent gene-by-obesity interactions present for each pair of lipids and environmental factors. Genetic contributions to the risk of TG abnormalities are described in Figure 3.a, 3.b, and 3.c (Table 3). The detected genetic factors accounted for approximately 38.3% of the total variance of abnormal TG risk after adjusting for age, age^2, and sex. Genetic markers located on genome-wide dense SNP microarrays accounted for 18.4-26.4% of the overall variance of the risk of TG abnormalities. About 36.6% of the total heritability was due to 40 independent SNPs identified by GWASs; genetic contributions increased to 47.1% when we considered

the interactions of *APOA5* or *BUD13* with WC. The total genetic impacts, in similar, increased from 39.3% to 58.0% when we considered both marginal associations and newly found genetic interactions attributable to WHR. For Caucasians, the additional heritability of TG due to the interactions of GxE variants with WC or WHR was 5.8% and 9.1%; the gain was 10.6% and 18.7% for Koreans, respectively.

Genetic contributions to the risk of abnormal elevation of Remnant-C are described in Figure 3.d (Table 3). The detected genetic factors explained approximately 48.6% of the total variance after adjusting for age, age^2, and sex. Genetic markers genotyped on SNP microarrays accounted for 11.3-14.2% of the overall variance for Remnant-C. About 38.5% of the total heritability was explained by 59 GWAS-identified SNPs only. When marginal associations and interactions of *APOA5* or *BUD13* with WHR, which change abnormal Remnant-C risk were considered, the genetic contributions increased to 47.8%; there were 9.3% differences between marginal and total genetic impacts. For Caucasians, the additional heritability of Remnant-C was just 5.1%.

3. Discussion

One of the main purposes of human genome studies is to personalize treatments and health guidelines due to one's genetic constitution. GWISs are approaches intended for achieving this end, particularly when genetic loci interacting with modifiable risk factors are investigated at genome-wide levels. Such studies permit the identification of higher-risk or lower-risk individuals depending on changes in known risk factors.

In this study, we identified novel and known genes interacting with obesity traits for changing the risk of dyslipidemia. We also replicated our findings using independent Korean genome cohorts and assessed how much phenotypic variance or heritability was additionally explained by considering the gene-by-obesity interactions.

Our study has focused on increasing power to detect gene-by-obesity interactions by applying a variety of strategies for testing GxEs. We carried out emerging exhaustive scans and two-step methods in parallel because each analytical GxE model provided differential power to find interactions, mainly according to marginal genetic and GxE effects. We tested interactions of SNPs at a genome-wide scale with various obesity traits, including Korean-specific parameters defined by additional ranges of BMI and WC. Furthermore, we adopted liberal cut-offs and stepwise penalties due to marginal genetic *p*-values as well as the standard genome-wide significance level to find gene-by-obesity interactive loci influencing the risk of dyslipidemia. For GxE studies, type 1 errors are generally considered to be less problematic than possible underpowered findings (105); applying multiple analytical models is advantageous to identify GxEs at a genome-wide level. By replication and stratified analyses for a candidate region localized by previous studies, we can further verify the identified interactions.

Our findings reveal a genome-wide set of SNPs with a wide range of marginal effects on the risk of dyslipidemia. We identified novel GxE variants located on *SCN1A* and *SLC12A8* with few or no direct association with lipid parameters as well as gene-by-obesity interactions related to lipid-associated genes reported in previous GWASs on

lipids: *APOA5*, *BUD13*, *ZNF259*, and *HMGCR*. We identified *SCN1A* and *SLC12A8* through exhaustive CO analyses, while all other GxEs attributable to lipid-associated loci were detected by using two-step methods, such as CT1, CT2, and EDGxE. These trends are consistent with the results of earlier simulation studies on statistical power for GxE detection, which showed that exhaustive CO analysis is more powerful than other two-step methods when the marginal effects of genetic variants are small (30). To our knowledge, *SCN1A* and *SLC12A8* have not been reported in previous studies to be associated with any lipid parameters.

We replicated our findings in four independent Korean genome cohorts; one strength of using cohorts formulated on identical protocols is the ability to examine gene-by-obesity interactions with high-quality health-related outcome variables, genetic and environmental factors. In addition, conducting a meta-analysis with the independent Korean cohorts permitted the estimation of more precise effects of susceptibility loci interacting with obesity traits. We also classified study populations into three groups according to the number of risk alleles at GxE loci and compared the changes in lipid levels when BMI, WC, and WHR increased by one unit among the three groups. The identified gene-by-obesity interactions were ascertained from another point of view by this comparison; the increment of the number of risk alleles worsened the changes in lipids due to the elevation of obesity indices.

Although generating interesting findings, our approaches for testing gene-by-obesity interactive effects on lipid profiles have some limitations. Our study did not include

GxEs due to low-frequency and rare variants (MAF<0.01); we also did not use other essential obesity indices, such as body fat percentage and visceral fat level. We only focused on GxE effects due to a set of common variants since our study populations did not include enough information for low-frequency and rare variants. In addition, current analytical methods do not offer adequate power to detect GxE effects of rare variants. The latest approaches using gene-set analyses and the sum of powered score tests are also limited to test GxEs at a variant-by-variant level (134, 135). Some rare variants in *NPC1L1*, however, are known to be related to cholesterol absorption and LDL-C levels (136), and the interplay between rare variants and obesity traits might play a role in regulating lipid levels.

Besides, our new findings primarily concern GxEs based on indirect obesity indices; BMI, WC, and WHR are surrogate measurements of overall and abdominal adiposity (137). Other vital measures of adipose tissue distribution, including visceral fat level and body fat percentage, have been reported to be related to higher risks of CVD and metabolic syndrome in large-scale epidemiological studies (138-140); these indices, however, were not addressed in this study. Even though we used commonly accepted guidelines of the NIH and KSSO (121, 122), the cut-offs to define obesity traits were somewhat arbitrary. Considering the evidence that a cardio-metabolic abnormality is more closely linked with body shape or body fat distribution than with conventional obesity indices (141, 142), interactions of genetic susceptibility loci of dyslipidemia with indicators that directly reflect adiposity warrant greater concern.

Our ability to extend the novel GxE findings from Korean populations to other ethnic groups is limited by the differences in MAFs of each variant, distributions of obesity traits, and prevalence of dyslipidemia. Our findings were estimated and reconfirmed in four independent cohorts sharing protocols to measure phenotypes and genotypes. The detected gene-by-obesity interactions on dyslipidemia might not be supported if racial differences in lipids and distributions of genetic and environmental factors are considered. *ZNF259* marked by rs2075291, for example, could be a useful target for managing TG in Korean population; the *ZNF259*-by-WHR interactive impact on the risk of TG abnormalities was 3.4%. This locus, however, is not a suitable therapeutic target for the other ethnic groups; the minor allele is infrequent for South Asians and too rare for Europeans, Americans, and Africans (Table 3). Conversely, some minor findings in this study could be useful in other ethnic groups.

Many human traits or complex diseases are considered consequences of both genetic and environmental factors. Thus, GxE analyses may hold the key to further insights on disease biology and the development of better prediction models. Our exploration of GxEs at a genome-wide level in Koreans revealed novel genetic susceptibility loci of dyslipidemia interacting with modifiable obesity traits. Our results were replicated in independent genome cohorts and confirmed by comparing changes in lipid levels attributable to an increment of obesity for each genetic subgroup. Compared to lipid-associated loci having only marginal genetic effects, the inclusion of gene-by-obesity interactive loci explained more of the total and genetic variances of each lipid. Based on the different MAFs between Caucasians and Asians, besides, Asians have a higher risk of dyslipidemia, particularly for TG, even with a small increase in obesity traits.

These newly identified genetic interactions with obesity traits can be used to classify individuals into higher-risk or lower-risk groups and to personalize health guidelines for managing lipid and obesity traits according to the genetic constitution.

Chapter IV.

A Genome-Wide Search for Gene-by-Lifestyle Interaction Loci of Hypertension

1. Materials and Methods

1.1. Participants

A total of 18,025 individuals of Korean descent from four independent cohort studies with a genome-wide set of variants were included in this gene-by-lifestyle interaction study on HBP: 4,637 individuals from the Ansan cohort, 4,205 individuals from the Ansung cohort, 3,700 individuals from the urban cohort, and 5,483 individuals from the rural cohort. Participants who have suffered cancer or diabetes or any CVDs were excluded from this study; people taking any antihypertensive drugs were considered as patients with hypertension (Supplemental Figure S9). The baseline characteristics of each cohort study are described in Table 4; a total of 15,954 people were included in this study on hypertension.

Participants in the Ansan and Ansung cohort, the reference set, were aged about 40-69 years and recruited from industrialized suburban and rural regions of the Republic of Korea. Participants in the urban and rural cohorts, the replication set, on the other hand, were aged over 40 years; they were recruited from medical institutions located in urban and rural areas of Korea. These four Korean genome cohort studies are part

of the KoGES, an ongoing population-based cohort study initiated in 2001 to provide evidence of chronic diseases among Koreans. The research protocols and data in this study have followed the Declaration of Helsinki principles; this study was approved by the IRB of Seoul National University (IRB number: E1805-003-001).

1.2. Measurements

Data about health status, health-related behaviors, medical histories, and medications were collected through standardized questionnaires. Trained experts at each medical center conducted anthropometric measurements, specimen collection, and laboratory tests. All participants provided informed consent for the baseline data and specimens; more detailed protocols were presented in previous reports (118, 119). SBP and DBP were assessed three times on both arms to make the valid measures; the higher value was confirmed as an individual's BP level. Detailed protocols for measuring BP have followed the AHA guidelines for managing HBP (78). We determined mean arterial pressure (MAP) as the sum of DBP and PP divided by three; Mid-BP was the average of SBP and DBP. We decided an individual's habits of cigarette smoking and alcohol consumption through standardized questionnaires. BMI or WHR, on the other hand, were calculated using directly measured height, weight, WC, and HC.

1.3. Phenotypes

We defined hypertension based on clinical cut-offs of high-risk CVD groups reported in the AHA guidelines (78): HBP-S1 ($130 \leq SBP < 140$ mmHg or $80 \leq DBP < 90$ mmHg) and HBP-S2 ($SBP \geq 140$ mmHg or $DBP \geq 90$ mmHg). Individuals who have taken any

antihypertensive drugs were considered as patients with HBP in statistical analyses. We decided behavioral traits of smoking using self-report of cigarette smoking: ever and current smoking. We also decided behavioral traits of drinking using self-report of alcohol consumption: ever drinking, current drinking, moderate drinking, low-risk drinking, heavy drinking, and binge drinking (Supplemental Table S1). We followed clinical guides of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to decide cut-off points for alcohol consumption. We defined obesity traits based on clinical guidelines of the NIH and KSSO (121, 122): underweight, overweight class 1, overweight class 2, obesity, abdominal obesity class 1, abdominal obesity class 2, and abdominal obesity based on WHR (Supplemental Table S1).

1.4. Genotype Information

We used the following genome-wide dense SNP microarrays for generating genotype data: the Affymetrix Genome-Wide Human SNP Array 5.0 for the Ansan and Ansung cohorts, version 6.0 for the urban cohort and a part of the rural cohort (n=1,816), and the Illumina HumanOmni1-Quad BeadChip for the rest of the rural cohort (n=3,667). Any marker violating Hardy-Weinberg equilibrium (p-value<$1x10^{-6}$), with genotype call rates below 95%, or with MAFs below 0.01 were excluded. After quality control, the remaining SNPs were imputed by using the haplotypes phase I in NCBI build 37 (GRCh37/hg19) of the Asian references from the 1000 Genomes Project. SHAPEIT2 and IMPUTE2 were used for the haplotype phasing and imputation (123, 124). SNPs with quality scores higher than 0.6 were retained, yielding 4,780,608 variants for the reference set and 5,729,661 variants for the replication set. A total of 3,914,038 SNPs were selected as the final genetic markers after comparing each cohort.

1.5. Statistical Analyses

The risk of hypertension was adjusted for age, age^2, sex, and BMI to test interactions of GxE SNPs with traits of smoking or drinking; the logarithm of OR was corrected by using a logit model. For gene-by-obesity interactions, on the other hand, HBP risk was adjusted for age, age^2, and sex; the logarithm of OR was also corrected by using a logit model. We conducted marginal DG and EG analyses for the 3.9 million SNPs before GWISs. Genetic markers associated with both BP and environmental factors (p-value$<1x10^{-3}$) were excluded to reduce potential pleiotropy.

We conducted exhaustive scans, such as CC, CO (106), and EB tests (107), and two-step methods (DG1, DG2 (110), EG2 (111), H2 (105), CT1, CT2 (112), and EDGxE (30)) in parallel. After finding novel GxE variants, we applied the standard genome-wide significance level (p-value$<5x10^{-8}$) for exhaustive scans. For step-1 of the DG1, DG2, EG2, and H2, we assumed a screening cut-off of $1x10^{-4}$; the subset of screened SNPs was examined for step-2 at a more liberal cut-off (0.05 divided by the number of screened SNPs) (105). We applied weighted hypothesis testing methods in step-2 of CT1, CT2, and EDGxE rather than testing only variants passing a screening step; stepwise penalties according to the marginal p-value were applied for SNPs in step-2 (125). One of a pair of the identified SNPs was removed if the LD was greater than 0.5, which means a VIF was greater than 2, for LD clumping. We found novel GxEs by using the reference set; all detected GxEs were confirmed by using the replication set. We used PLINK (126), METAL (127), and R in the analyses.

1.6. Methods of Evaluating Impacts

We used the simplified equation $2p(1-p)[\log(OR)]^2$ to estimate the genetic variances due to genetic susceptibility SNPs; p is the MAF of a variant and OR is the estimated marginal effect (128). The contribution of GxE loci, on the other hand, was estimated using the equation $2p(1-p)[\log(OR_G)]^2/V_P+2ep[(1-p)+2p(e-1)^2][\log(OR_{GxE})]^2/V_P$; in this equation, V_P is the phenotypic variance, e is the prevalence of an environmental factor, OR_G and OR_{GxE} are estimated genetic and GxE effects. We estimated the total HBP heritability from the Healthy Twin Study (130, 131) by using GenABEL (129). We also used GCTA (132) to estimate the SNP-based heritability due to the GWAS-variants on SNP microarrays. We cited the prevalence of HBP-S1 and HBP-S2 using information from the KNHANES to transform the estimate of variance explained on the observed scale to that on the underlying scale (143). According to the KNHANES data, the prevalence of HBP-S1 and HBP-S2 are 49.2% and 30.4%, respectively.

2. Results

2.1. Characteristics of the Study Populations

Table 4 describes the baseline characteristics of the participants in four independent Korean genome cohorts. We presented age, sex, obesity-related traits, and BP-related traits adjusted for age, age^2, sex, and BMI. As mentioned above, SBP and DBP have been directly measured three times from each participant; the highest BP level of the three measures was confirmed as the valid level for each SBP or DBP. MAP, PP, and Mid-BP, on the other hand, have been indirectly assessed: 1) MAP is the sum of DBP

and PP divided by three, 2) PP is the value of SBP minus DBP, and 3) Mid-BP is the average of SBP and DBP.

2.2. Identification of Gene-by-Lifestyle Interactive Loci

We identified 62 SNPs showing genome-wide significant GxE effects on the risk of hypertension with at least one of the lifestyle factors, including two traits of cigarette smoking, six traits of alcohol consumption, and seven traits of obesity (Supplemental Table S8). After LD clumping due to genetic contributions of each SNP to HBP risk, we detected 24 gene-by-lifestyle interactions of novel variants (*BRAP*, *SH2B3*), BP-associated SNPs (*ATP2B1*), alcohol-associated variants (*ALDH2*, *CUX2*, *HECTD4* (*C12orf51*), *MYL2*, *OAS3*), and SNPs related to obesity (*ST5*). Table 5 describes the marginal and gene-by-lifestyle interactive effects of the newly identified variants on the risk of hypertension; detailed results are presented in Supplemental Table S8. As shown in Supplemental Table S9, we estimated genomic inflation factors (λ) of each genetic effect, such as marginal, main SNP, and gene-by-lifestyle interactive effects, in each logistic regression model for testing DG associations and GxEs.

Figure 4 (Supplemental Table S10) describes the risk of HBP-S1 or HBP-S2 for each genetic and environmental factor; we estimated ORs as the ratio of HBP probability occurring in exposed groups (G≠0 or E≠0) to the probability for non-exposed groups (G=0 and E=0). *DCC* marked by rs9950661 interacted with ever smoking to change the risk of HBP-S1; CT1 and CT2 methods observed the variant. The OR_D, OR_G, and OR_{GxE} for the interaction between *DCC* and ever smoking were 0.87 (95% CI, 0.85-

0.90), 0.89 (95% CI, 0.86-0.92), and 0.90 (95% CI, 0.86-0.95). Multiplicative effects were described in Figure 4.a (Supplemental Table S10.a). For common homozygous, the effect was 1.22 (95% CI, 1.17-1.27); the effect was 1.16 (95% CI, 1.11-1.21) and 1.23 (95% CI, 1.12-1.35) for heterozygous and rare homozygous genotypes.

RPH3A marked by rs886476 showed antagonistic effects on the risk of HBP-S1 due to low-risk drinking. For this interaction, the OR_D, OR_G, and OR_{GxE} were 0.91 (95% CI, 0.89-0.94), 0.93 (95% CI, 0.91-0.96), and 0.64 (95% CI, 0.60-0.68), respectively. As shown in Figure 4.b (Supplemental Table S10.b), the multiplicative effect of low-risk drinking was 1.27 (95% CI, 1.19-1.34), 1.13 (95% CI, 1.05-1.22), and 1.11 (95% CI, 0.94-1.30) for common homozygous, heterozygous, and rare homozygous.

MYL2 marked by rs4766517, on the other hand, had synergistic effects on the risk of HBP with heavy drinking. The locus already had been reported to be associated with alcohol consumption in previous GWASs (144). For the GxE, the estimated OR_D was 1.00 (95% CI, 0.97-1.02); OR_G and OR_{GxE} were estimated to be 0.97 (95% CI, 0.94-1.00) and 1.38 (95% CI, 1.31-1.45). As described in Figure 4.c (Supplemental Table S10.c), the multiplicative effect of heavy drinking was 1.14 (95% CI, 1.05-1.24) for individuals with two wild-type alleles at rs4766517. The effects, however, increased with the number of minor alleles; the effects were 1.21 (95% CI, 1.14-1.27) and 1.33 (95% CI, 1.24-1.42) for heterozygous and homozygous minor alleles.

Antagonistic effects were induced by the interaction between rs79977578 located on

KLF4 and moderate drinking for the risk of hypertension. The estimated OR_D, OR_G, and OR_{GxE} were 0.97 (95% CI, 0.93-1.01), 1.19 (95% CI, 1.13-1.26), and 0.60 (95% CI, 0.55-0.66) for the interplay, respectively. As shown in Figure 4.d (Supplemental Table S10.d), the multiplicative effect on HBP-S1 was 1.06 (95% CI, 1.02-1.09) for individuals having two wild-type alleles, 0.81 (95% CI, 0.74-0.87) for heterozygous, and 0.95 (95% CI, 0.70-1.30) for rare homozygous genotypes.

For HBP-S2 risk, we detected four novel gene-by-obesity interactions; we could not find any loci interacting with cigarette smoking or alcohol consumption. *ST5* marked by rs140343181 has synergistic effects with obesity on the risk of HBP-S2; the OR_D, OR_G, and OR_{GxE} were 0.90 (95% CI, 0.79-1.02), 0.79 (95% CI, 0.69-0.91), and 4.23 (95% CI, 3.25-5.50), respectively. *RP11-981P6.1* marked by rs1689040 had a risky GxE effect due to obesity; the OR_D, OR_G, and OR_{GxE} were 0.86 (95% CI, 0.83-0.88), 0.85 (95% CI, 0.82-0.87), and 1.34 (95% CI, 1.18-1.53). Multiplicative GxE effects of obesity for common homozygous, heterozygous, and rare homozygous were 1.69 (95% CI, 1.44-1.99), 2.18 (95% CI, 1.90-2.51), and 2.37 (95% CI, 1.87-3.00); more detailed features were described in Figure 4.e (Supplemental Table S10.e).

ATP2B1, a locus known to be associated with BP (90, 145), gave a synergistic effect with abdominal obesity on the risk of HBP-S2. For the interaction between *ATP2B1* and abdominal obesity, the OR_D was 0.85 (95% CI, 0.83-0.88); OR_G and OR_{GxE} were estimated to be 0.82 (95% CI, 0.79-0.86) and 1.13 (95% CI, 1.07-1.20). As described in Figure 4.f (Supplemental Table S10.f), the multiplicative GxE effect of abdominal

obesity was 1.47 (95% CI, 1.35-1.61) for people having two wild-types at rs2681472. The effect sizes of abdominal obesity increased with the number of risky alleles; the effects were 1.63 (95% CI, 1.50-1.78) and 1.73 (95% CI, 1.47-2.03) for heterozygous and homozygous risky alleles.

MYL2 also showed synergistic effects on HBP-S2 risk with abdominal obesity based on WHR. For the interaction, the OR_D was 0.89 (95% CI, 0.86-0.93); OR_G and OR_{GxE} were 0.80 (95% CI, 0.74-0.86) and 1.20 (95% CI, 1.10-1.32), respectively. As shown in Figure 4.g (Supplemental Table S10.g), the multiplicative effect due to abdominal obesity was 1.78 (95% CI, 1.66-1.91) for people with two wild-types at rs12229654. The effect sizes due to abdominal obesity increased with the number of minor alleles; the effect was estimated to be 1.95 (95% CI, 1.72-2.21) and 2.68 (95% CI, 1.65-4.35) for heterozygous and homozygous minor alleles.

2.3. Genetic Contribution of Gene-by-Lifestyle Interactions

Table 6 presents the contributions due to marginal associations and gene-by-lifestyle interactions to the risk of hypertension. We suggest the proportion of total heritability for each stage of hypertension by 1) GWAS-identified SNPs, 2) novel GxE loci, and 3) the combined set of both BP-associated and gene-by-lifestyle interactive variants, so-called the total genetic impact. The total and SNP-based HBP-S1 heritability was approximately 39.3% and 14.6-26.7%, after adjusting HBP-S1 risk by age, age^2, and sex. The genetic contribution increased with a difference between GWAS-identified and total genetic impact of 0.3-2.1% if we considered both marginal associations and

interactions of GxE variants with cigarette smoking or alcohol consumption. We also described the genetic contribution attributable to marginal associations and gene-by-lifestyle interactions in Figure 5.

For HBP-S2 risk, there were four novel gene-by-obesity interactions of variants with GxE impacts of 0.2-1.2%. The total and SNP-based heritability of HBP-S2 was about 29.0% and 16.7-25.9% after adjusting the risk of hypertension by age, age^2, and sex (Table 6). As shown in Figure 5, the genetic contribution increased if we considered both marginal genetic and gene-by-obesity interactive loci, with differences between the impact due to the GWAS-identified variants and total genetic impact of 1.1-1.2%. Unfortunately, we could not detect any genetic variants for HBP-S2 interacting with cigarette smoking or alcohol consumption.

Some variants show racial differences in MAFs and GxE impacts on the risk of HBP: rs10849933 (*CUX2*), rs79977578 (*KLF4*), and rs12229654 (*MYL2*). *CUX2*, marked by rs10849933, for example, shows a small impact for Koreans compared with other ethnic groups, such as Europeans or Americans. The minor allele is rare for Koreans; the frequency is 0.32 for Koreans, 0.83 for Europeans, and 0.83 for Americans. MAF of rs79977578 near *KLF4*, conversely, is extremely low for Americans or Europeans or Africans; the frequency is 0.03 for Americans and approaching 0.00 for Europeans and Africans. Thus, *KLF4* shows the more significant GxE impacts for Koreans, East Asians, and South Asians. For gene-by-obesity interactions on HBP-S2, on the other hand, *MYL2* has the more significant impact for Koreans and East Asians compared

with other ethnic groups; for South Asians, Europeans, Americans, and Africans, the minor allele of rs12229654 is extremely rare (Table 6).

3. Discussion

We identified novel and known genes modifying the risk of hypertension for Koreans by interacting with lifestyle factors, such as cigarette smoking, alcohol consumption, and obesity. Our findings were replicated in four independent Korean cohort studies with a genome-wide set of variants. We also assessed how much phenotypic variance or heritability of HBP was additionally explained by considering the identified gene-by-lifestyle interactions. About 0.3-2.1% of the heritability, besides, was additionally explained by considering both marginal genetic associations and genetic interactions with cigarette smoking or alcohol consumption or obesity.

In this study, we have identified several GxE variants with a wide range of marginal genetic effects on the risk of hypertension; our findings have covered a genome-wide set of SNPs. There were novel GxE markers located on *BRAP* and *SH2B3* with little or no direct genetic associations with BP parameters as well as genetic loci associated with BP (*ATP2B1*), alcohol consumption (*ALDH2*, *CUX2*, *HECTD4*, *MYL2*, *OAS3*), and obesity (*ST5*); these variants have already been reported in previous GWASs (90, 144, 145). We have detected most GxE variants through exhaustive CO tests; in other word, the identified SNPs had a weak marginal effect on HBP and had a rare chance to be detected through standard CC tests. In general, CO analyses give much greater

power of testing interactions than the other exhaustive scans (30). To our knowledge, *BRAP* and *SH2B3* have not been previously reported in GWASs on any BP traits.

In this GWIS, we have focused on increasing the power to test interactions between genes and lifestyle factors by applying various analytical GxE models. We conducted several exhaustive scans and two-step approaches as possible; each statistical model provided differential power to detect GxEs across a range of magnitudes for marginal genetic and interactive effects of genetic susceptibility loci. We explored interactions of a genome-wide set of variants with several behavioral traits of cigarette smoking, alcohol consumption, and obesity, including Korean-specific indices determined by additional ranges of BMI and WC. As well as the standard genome-wide significance level (p-value$<5\times10^{-8}$), we also adopted liberal thresholds and stepwise penalties due to marginal p-values for the detection of gene-by-lifestyle interactive loci modifying the risk of hypertension for Koreans.

Although the replication of novel findings has not been widely required for reporting GxEs, we replicated our findings in four independent Korean genome cohort studies. We believe replications in GxE studies are as important as in GWASs, especially for GWISs; the possible type 1 errors or false-positive findings induced by using various analytical GxE models need to be verified by replications and stratified analyses for candidate regions localized by previous researches. The four Korean cohorts, on the other hand, have shared the research protocols, phenotypic data, and genotypes; one strength of using cohorts sharing identical protocols is the ability to test interactions

with high-quality health outcomes, genetic and environmental factors. Moreover, we conducted meta-analyses with the Korean cohort studies; these approaches permitted the more precise effect estimates of BP-loci interacting with lifestyle factors.

There are some limitations in this study; first of all, we only focused on the gene-by-lifestyle interactions due to a set of common variants since our study populations did not include enough information for rare variants (MAF<0.01). Unfortunately, current statistical methods do not provide adequate power to detect GxEs attributable to low-frequency or rare variants; the latest methods based on gene-set analyses and the sum of powered score tests are also limited for testing GxEs, variant by variant (134, 135). There is the possibility that rare genetic markers modifying HBP risk due to lifestyle may exist; most of the identified GxE loci in this study had a weak marginal genetic effect on the risk of HBP-S1 or HBP-S2.

Furthermore, our findings primarily concern interactions based on indirect measures of cigarette smoking, alcohol consumption, and obesity. We decided behavioral traits of cigarette smoking or alcohol consumption by using self-reports only; daily intakes of alcohol, the main index for determining behavioral traits of alcohol consumption, were also calculated by using a self-reported alcohol intake. For obesity, on the other hand, we considered surrogate measures of overall and abdominal adiposity, such as BMI, WC, and WHR (137). We did not consider other vital indices, such as body fat percentage and visceral fat level; these parameters had been reported to be related to higher CVD risk and metabolic syndrome (138-140). Even though we have followed

commonly accepted guides of the NIAAA, NIH, and KSSO to define environmental factors (121, 122), the thresholds were somewhat arbitrary. If we had any indicators which directly reflect lifestyle factors, such as chemicals in tobacco, body or visceral fat level, we could determine the more precise indices of each environmental factor; it may provide the higher power to detect GxEs.

Our novel findings were estimated and reconfirmed in four Korean genome cohorts formulated on identical protocols. The identified gene-by-lifestyle interactions were limited to be applied to other ethnic groups having differences in MAFs of each GxE variant, distributions of lifestyle factors, and prevalence of HBP. *ALDH2* marked by rs112605264, for example, could be the more useful therapeutic target for managing HBP for Europeans than for Koreans; the variant is most common for individuals of European descent (MAF=1.00). For gene-by-obesity interactions, on the other hand, rs12229654 located on *MYL2* shows the greater impact for Koreans and East Asians compared with other ethnic groups; the minor allele is extremely rare for Europeans, Americans, Africans, and South Asians (MAF=0.00). It may be useful in the Korean and East Asian populations but not for the other ethnic group.

Human complex diseases are known to be related to both genetic and environmental factors; we may have further insights on disease biology and develop more accurate prediction models by exploring GxEs. GWISs are approaches particularly designed for the main purposes of human genome studies: to personalize treatment and health guidelines according to an individual's genetic constitution. Such studies permit the

identification of higher-risk or lower-risk groups depending on a known modifiable risk factor. Our study on gene-by-lifestyle interactions has revealed variants of HBP interacting with behavioral factors, such as cigarette smoking, alcohol consumption, and obesity. Compared to genetic loci having marginal effects only, the inclusion of GxE variants clearly explained more of the total and genetic variances of HBP. These newly identified gene-by-lifestyle interactions could be used to classify individuals into different risk groups and to give personalized guidelines for managing HBP and lifestyle factors according to the genetic constitution.

Chapter V.

A Genome-Wide Interaction Scan for Lipids and Blood Pressure Levels

1. Materials and Methods

1.1. Participants

A total of 18,025 individuals from four independent Korean genome cohorts, as same as the population of our previous GWISs, were included in this study on quantitative lipids and BP levels: individuals from the Ansan cohort (n=4,637), the Ansung cohort (n=4,205), the urban cohort (n=3,700), and the rural cohort (n=5,483). For the study on lipid levels, individuals who have suffered cancer or diabetes were excluded; we also excluded people taking any lipid-lowering drugs (Supplemental Figure S12). In the study on BP levels, individuals who have experienced cancer or diabetes or CVD were excluded. For people taking any kind of antihypertensive medication, we added 10 mmHg and 5 mmHg to observed SBP and DBP levels, respectively (90, 146, 147) (Supplemental Figure S13). Table 7 shows the baseline characteristics of the Korean genome cohorts for each quantitative GWIS. A total of 15,754 people were included in the GWIS for lipids; a total of 15,954 individuals, on the other hand, were included in the GxE study on quantitative BP levels.

People, aged 40-69 years, were included in the Ansan and Ansung cohorts; they were

recruited from industrialized suburban and rural areas of the Republic of Korea. For the urban and rural cohorts, on the other hand, individuals, aged over 40 years, were recruited from medical centers located in urban and rural regions of Korea. The four Korean cohorts are part of the large-scale population-based cohort study, the KoGES. The research protocols and data in these studies followed the Declaration of Helsinki principles and were approved by the IRB of Seoul National University (IRB number: E1805-003-001).

1.2. Measurements

The overall protocols for this study were also described in our previous studies; more detailed protocols to collect an individual's data on health status, behaviors, medical, and medication histories are described in previous reports (118, 119). Total-C, HDL-C, and TG levels were measured by using traditional enzymatic methods in the blood samples drawn after an 8-hour fast. We calculated LDL-C levels by the Friedewald's formula (120); Remnant-C levels were determined as a quantitative level of Total-C minus HDL-C minus LDL-C (42, 44). SBP and DBP levels, on the other hand, were measured as instructed in the AHA guides (78). Behavioral factors, such as cigarette smoking and alcohol consumption, were assessed by the standardized questionnaire. We calculated obesity indicators, such as BMI and WHR, by using directly measured height, weight, WC, and HC.

1.3. Phenotypes

We used the following quantitative lipids for testing gene-by-obesity interactions at

a genome-wide scale: Total-C, HDL-C, LDL-C, TG, and Remnant-C (mmol/L). For this study, we excluded individuals who have suffered cancer or diabetes; individuals taking any lipid-lowering medications were also excluded. For the gene-by-lifestyle interaction study on BP levels, we used SBP and DBP (mmHg) as outcome variables. We also excluded individuals who have experienced cancer or diabetes or any CVDs. For people taking any antihypertensive drugs, we added 10 mmHg to observed SBP and 5 mmHg to observed DBP (90, 146, 147). The same behavioral factors with our previous GWISs were used in this GWIS: cigarette smoking (ever, current smoking), alcohol consumption (ever, current, moderate, low-risk, heavy, binge drinking), and obesity (underweight, overweight class 1, 2, obesity, abdominal obesity class 1, 2, or abdominal obesity based on WHR). The detailed cut-off points for behavioral factors are described in Supplemental Table 1.

1.4. Genotype Information

Genome-wide dense SNP microarrays were used to create genotype information. We have already introduced the SNP microarrays in our previous GWISs: the Affymetrix Genome-Wide Human SNP Array version 5.0, 6.0, and the Illumina HumanOmni1-Quad BeadChip. We excluded any variant violating Hardy-Weinberg equilibrium (p-value$<1x10^{-6}$) or with genotype call rates below 95% or with MAF below 0.01. The remaining SNPs were imputed by the 1000 Genomes Project's haplotypes phase I in NCBI build 37 (GRCh37/hg19) of the Asian references. SHAPEIT2 and IMPUTE2 were used for phasing and imputation (123, 124). Only genetic variants with quality scores higher than 0.6 were retained, yielding 4,780,608 and 5,729,661 SNPs for the reference and replication set. A total of 3,914,038 variants having imputation quality

higher than 0.6 were selected as the final genetic variants after comparing each set.

1.5. Statistical Analyses

We carried out two independent GWISs in this study: GWISs for 1) gene-by-obesity interactions on quantitative TG and 2) gene-by-lifestyle interactions on quantitative BP levels. Compared with our previous GxE findings, we tested whether the different scales of outcome variables (continuous vs. dichotomous) had affected the results of GWISs. In the GWIS for TG, we transformed continuous TG, a non-normalized trait, into a logarithmic scale and adjusted the transformed TG for age, age^2, sex, and each obesity trait, one by one. In the GWIS for BP, on the other hand, SBP and DBP were adjusted for age, age^2, sex, and BMI; we adjusted each BP for age, age^2, and sex for testing gene-by-obesity interactions. We also carried out DG and EG tests for the 3.9 million SNPs before quantitative GWISs. Genetic markers associated with both one of the outcomes and environmental factors (p-value<1x10^{-3}) were excluded to reduce the potential pleiotropy.

We conducted CC, DG2 (110), EG2 (111), H2 (105), and EDGxE (30) methods, the analytical approaches that could be extended to GWISs for quantitative phenotypes, in parallel. After detecting novel GxE variants, we applied the standard genome-wide significance level (p-value<5x10^{-8}) for a CC analysis. For the screening step of DG2, EG2, and H2 analyses, we assumed a screening cut-off of 1x10^{-4}; the subset of SNPs passing step-1 was tested for step-2 at the more liberal threshold (0.05 divided by the number of screened SNPs) (105). We applied weighted hypothesis testing in step-2

of EDGxE rather than testing only variants passing step-1; stepwise penalties due to the marginal *p*-value were applied for each variant in step-2 (125). One of the pair of identified SNPs was removed for LD clumping. We identified novel GxEs using the reference set; all the identified interactions were confirmed using the replication set. We used PLINK (126), METAL (127), and R in the analyses.

2. Results

2.1. Identification of Gene-by-Obesity Interactions on TG Levels

We conducted GWISs for gene-by-obesity interactions on quantitative lipid levels in Supplemental Table S11. We compared the identified GxE loci of TG with the results from our previous study in Table 8; we newly found four genetic markers located on *APOA5* and *BUD13* interacting with BMI. They had strong marginal genetic effects on TG: rs2075291 (P=3.52x10^{-76}) and rs651821 (P=2.42x10^{-140}) located on *APOA5*, rs2000571 (P=9.70x10^{-25}) and rs2041967 (P=6.59x10^{-31}) located on *BUD13*. Except for rs2041967 (r^2=0.20), all the detected SNPs were in LD (r^2≥0.50) with the variant reported in our previous study, rs1558860 near *BUD13*. Unfortunately, we could not find any genetic interactions with WC or WHR on quantitative TG levels. Genomic inflation factors (λ) of marginal, main SNP, and interactive effects on TG levels were suggested in Supplemental Table S12.

Compared with the result from our research on dyslipidemia, directions of marginal

and main SNP effects were consistent with directions of OR_D and OR_G; on the other hand, those of GxE effects were inconsistent with those of OR_{GxE} (Table 8). *BUD13* marked by rs2041967, for example, showed synergistic effects with BMI on the risk of abnormal TG; the OR_{GxE} was 1.11 (P=2.03x10^{-1}). For the genetic interaction with BMI on TG levels, however, the GxE effect was estimated to be 0.03 (P=2.03x10^{-1}) in the opposite direction. Conversely, *BUD13* marked by rs1558860 had antagonistic effects with BMI on the risk of abnormal TG elevation; the OR_{GxE} was estimated to be 0.80 (P=3.27x10^{-3}). For *BUD13*-by-BMI interactions on TG levels, however, the GxE effect was estimated to be 0.02 (P=1.46x10^{-1}) in the opposite direction.

2.2. Identification of Gene-by-Lifestyle Interactions on SBP Levels

We also carried out GWISs for gene-by-lifestyle interactions on continuous BP levels in Supplemental Table S13. We compared the identified GxE variants of BP with the results from our previous study on the risk of HBP in Table 9; we focused on genetic interactions with alcohol consumption, such as low-risk drinking or heavy drinking. As described in Table 9, we identified a novel variant near *BTF3P13* interacting with heavy drinking to modify quantitative SBP levels; the novel SNP of SBP located on *BTF3P13* was rs12501917 (P=1.75x10^{-8}). We could not find any genetic interactions with low-risk drinking on quantitative SBP levels. Genomic inflation factors (λ) were suggested in Supplemental Table S14; we estimated those of genetic effects on SBP levels due to marginal associations, main SNPs, and gene-by-lifestyle interactions.

Compared with our previous findings, the directions of marginal genetic effects were

completely consistent with those of OR_D; on the other hand, directions of main SNP and interactive effects were inconsistent with those of OR_G and OR_{GxE}. For example, *ALDH2* marked by rs112605264 showed a consistent trend in the directions of each effect. The OR_D, OR_G, and OR_{GxE} were 1.05 (P=6.68x10^{-2}), 1.03 (P=3.00x10^{-1}), and 1.41 (P=5.48x10^{-13}); the marginal, main SNP, and interactive effects were estimated to be 0.27 (P=1.37x10^{-1}), 0.22 (P=2.57x10^{-1}), and 0.42 (P=4.50x10^{-1}), respectively. On the contrary, *SH2B3* marked by rs11065905 showed synergistic effects with low-risk drinking on HBP-S1 risk; the OR_{GxE} was 1.46 (P=3.84x10^{-8}). For the interaction with low-risk drinking on SBP, the GxE effect was 0.19 (P=7.92x10^{-1}) in the opposite direction; trends in the directions of GxE effects were inconsistent.

3. Discussion

We conducted two independent GxE studies at a genome-wide scale: 1) a GWIS for gene-by-obesity interactions on quantitative lipid levels and 2) a GWIS for gene-by-lifestyle interactions on quantitative BP levels. We evaluated whether the differences in scales of outcome variables (continuous vs. dichotomous) had affected the results of our previous studies. In GWISs for quantitative TG scales, we newly detected four interactions of BMI with *APOA5* or *BUD13*. All the genetic variants were in LD with the findings from our previous studies, except for rs2041967 (r^2=0.20); we could not find any interactions due to WC or WHR. In GWISs for quantitative SBP scales, on the other hand, we identified only one SNP on *TSPAN5* at the standard genome-wide significance level; there were no gene-by-lifestyle interactions on quantitative DBP.

Even though we found fewer GxE variants of dyslipidemia or hypertension by using quantitative scales of outcome variables, this study is meaningful in that it extended some analytical GxE approaches to quantitative outcomes and compared the results between two different outcome scales. As reported in the earlier simulation study on the statistical power of detecting GxEs (30), CO analyses and any derivatives of CO tests, such as EB, CT1, and CT2, are optimized to test genetic variants having a weak marginal effect. We also ascertained that the direction of each genetic effect, such as the marginal, main SNP, and gene-by-lifestyle interactive effect, was estimated to be consistent regardless of the scales of outcome variables.

In the GWISs for dyslipidemia and HBP, we used dichotomous outcomes instead of using quantitative scales of outcomes because the following reasons would improve the statistical power. 1) Some analytical methods for testing GxEs use dichotomous traits as a prerequisite, such as CO and EB tests, and these analyses are optimized to identify genetic variants having weak marginal effects. 2) Some approaches, such as CC, DG2, EG2, H2, and EDGxE approaches, could be extended to continuous scales of outcomes, and these methods provide more power for SNPs with strong marginal effects (30). 3) In analyses of statistical interactions, quantitative scales are sensitive to distribution; it is well-known that some non-normal distribution may generate type 1 errors or false-positive results of interactions.

Actually, our approaches using dichotomous outcomes could cover the broader range of gene-by-obesity and gene-by-lifestyle interactive variants, having strong marginal

effects as well as weak marginal effects, than the GWISs using quantitative scales of TG and SBP (Table 8 and 9). Moreover, GWISs using dichotomous scales were even more powerful and gave consistent results of GxEs. As recommended in several GxE studies (30, 105), it is more important to use multiple analytical methods as possible to provide more power and generate consistent results for GxE analyses.

For genetic variants with weak marginal effects, a CO test could be the most intuitive approach to detect interactions; it is only valid when the assumption of independence between genes and environmental factors is satisfied. Under these assumptions, CO analyses provide more power to detect GxEs than the other exhaustive scans or two-step methods; we can also test potential interactions directly with this approach. For variants having moderate to strong marginal effects, an EDGxE method could be the most appropriate way to investigate genetic interactions with environmental factors at a genome-wide scale. This two-step method ensures sufficient power to find GxEs regardless of the magnitude of GxE effects of each genetic variant (30).

Chapter VI.

Summary and Conclusions

1. General Discussion

In this study, we investigated the genetic interaction with modifiable lifestyle factors, such as cigarette smoking, alcohol consumption, and obesity. We conducted GWISs for 1) gene-by-obesity interactions on dyslipidemia, 2) gene-by-lifestyle interactions on hypertension, and 3) gene-by-obesity and gene-by-lifestyle interactions on lipids and BP levels, respectively. Our GxE study is different from previous genetic studies, particularly GWASs, in several points. First of all, we have focused on the estimates of effect differences between subgroups stratified by each genetic and environmental factor, so-called the GxE effects, not the marginal genetic effects. Secondly, we have applied multiple analytical models as possible and verified the results by replications and stratified analyses; we have used four Korean genome cohorts formulated on the identical research protocol. Finally, we have suggested the additional heritability of each lipid and BP attributable to both marginal associations and genetic interactions with modifiable environmental factors.

Even though our research has complemented the earlier GWASs on dyslipidemia or hypertension, especially in terms of GxEs, there are some inherent limitations in our approaches for testing interactions on lipid profiles and BP traits. For genetic factors,

we have investigated only GxEs due to a set of common variants; genetic interactions due to low-frequency or rare variants (MAF<0.01) were not considered in this study. Unfortunately, there was not enough information for low-frequency and rare variants in our study populations. By considering the sample size requirement for the analysis on GxEs is further inflated to solve the problem of multiple comparisons at genome-wide levels (15, 105), GWISs based on low-frequency or rare variants require much larger sample sizes to detect genetic interactions with environmental factors. Current analytical approaches using low-frequency or rare variants, moreover, do not provide adequate power for testing interactions; the latest method based on gene-set and the sum of powered score analyses also has limitations in finding interactions at variant-by-variant levels (134, 135).

For environmental factors, on the other hand, the complexity of measuring exposures and assigning temporality need to be considered in GxE studies, especially based on the CC study design (21, 22). In this study, we determined environmental factors by using indirect measures. We decided behavioral traits of cigarette smoking based on self-reports; traits of alcohol consumption were also assessed by using a self-reported alcohol intake. Obesity traits, in addition, were surrogate measurements of overall or abdominal adiposity, such as BMI, WC, and WHR (137). Even though we have used repeated measures of each phenotype, environmental factors in this GxE study could be relatively unstable than genetic factors; it is hard to consider a fluctuation in each exposure, especially in CC studies. Unfortunately, the outcome variable, such as the risk of dyslipidemia or hypertension, associated with environmental factors may be influenced by not only the estimated exposures themselves but also the source or the

place or the temporality of environmental exposures (22). Current analytical models need to be improved by considering a mixed model allowing both fixed and random effects of environmental factors to clarify the temporality issues.

We have applied emerging analytical models as possible to find interactions between genetic and environmental factors at a genome-wide scale. Some methods for GxEs, however, were not included in this GWISs: 1) 2-*df* test (148, 149), 2) 3-*df* test (150), and 3) variance heterogeneity test (151). A 2-*df* analysis, the combination of DG and CC models in chapter II, tests the following joint null hypothesis: $\lambda_G=\beta_{GxE}=0$. A 3-*df* analysis, the combination of DG, EG, and CC models, tests the following hypothesis: $\lambda_G=\delta_G=\beta_{GxE}=0$. A variance heterogeneity analysis, on the other hand, tests inequality of variance between genotypes to prioritize SNPs for further analyses; the prioritized variants are tested for GxEs against other genetic or environmental factors (151). All the methods, such as 2-*df*, 3-*df*, and variance heterogeneity tests, provide differential power to detect interactions according to marginal genetic and GxE effects; we may find more interactions by applying these analytical methods in future studies.

The suggested analytical models were verified for achieving the nominal type 1 error rate, the alpha less than 0.05, and providing sufficient power in the simulation study with multiple scenarios (30). However, we did not estimate type 1 error rates and the statistical power of each analytical method in our study populations. We selected the union of identified SNPs from multiple analytical models for further verification, not the intersection of findings. As we did not consider the replication between analytical

methods, there could be possible type 1 errors or false-positive findings. We thought the possible false-positive findings could be filtered by comparing variants identified from the reference set with those from the replication set. To ensure adequate power of detecting GxEs, on the other hand, we applied multiple analytical methods, which covered a broad range of interactions due to genetic loci with strong marginal effects as well as weak marginal effects (Reference Table R2 and Figure R1).

2. Summary and Conclusions

Dyslipidemia and hypertension, one of the most prevalent health-related conditions for Koreans, are well-established CVD risk factors. Previous studies on the complex traits imply the possible roles of gene-by-obesity or gene-by-lifestyle interactions on the risk of dyslipidemia and hypertension. Current GWASs have identified more than 500 and 800 genetic loci of plasma lipids and BP levels, respectively. The identified variants, however, were mainly focused on individuals of European descent and only explained a small fraction of the total and genetic variances of each lipid and BP trait. Interactions between genetic and environmental factors are believed to be a potential source of the missing heritability. Even though GWASs have successfully identified dozens of genetic markers related to lipids or BP levels, the interaction structures are not well-known. We intended to search lipid-associated or BP-associated genetic loci modifying the effect of risk factors, such as cigarette smoking, alcohol consumption, and obesity, by applying extensive GxE analyses at a genome-wide scale.

In chapter III, we identified 55 SNPs showing genome-wide significant GxE effects on the risk of dyslipidemia with at least one of the obesity traits. After LD clumping, we identified about 20 gene-by-obesity interactions due to novel variants located on *SCN1A* and *SLC12A8*; we also detected lipid-associated variants located on *APOA5*, *BUD13*, *ZNF259*, and *HMGCR*, which have been reported in previous GWASs. For normal-weight individuals having no risk alleles (low-risk group), HDL-C decreased by 0.032 mmol/L (95% CI, 0.030-0.034 mmol/L) for each unit (1 kg/m^2) increase in BMI; a decrement of HDL-C was 0.039 mmol/L (95% CI, 0.035-0.043 mmol/L) for individuals with at least one risk allele (high-risk group) and 0.038 mmol/L (95% CI, 0.033-0.043 mmol/L) for upper 50% of the high-risk group (higher-risk group). The declining trends were far clearer in obese individuals; similarly, we ascertained that an increment of TG was different for each genetic subgroup, and the trends of change were clearer in individuals with obesity. The genetic contribution, on the other hand, was markedly higher when several independent gene-by-obesity interactive variants were present for each pair of lipid traits and environmental factors. About 36.6% of the TG heritability, for example, was due to 40 independent GWAS-identified SNPs only; genetic contributions increased to 47.1% when we considered the interactions of *APOA5* or *BUD13* with WC. For Caucasians, the additional heritability of TG due to the genetic interaction with WC was 5.8%; the gain was 10.6% for Koreans.

In chapter IV, we identified 62 SNPs showing genome-wide significant GxE effects on the risk of hypertension with lifestyle factors, such as cigarette smoking, alcohol consumption, and obesity traits. 24 gene-by-lifestyle interactions remained after LD clumping: interactions due to 1) novel variants (*BRAP* and *SH2B3*), 2) BP-associated

variants (*ATP2B1*), 3) alcohol-associated variants (*ALDH2*, *CUX2*, *HECTD4*, *MYL2*, *OAS3*), and 4) obesity-related variants (*ST5*). The genetic contribution, on the other hand, increased with differences between GWAS-identified and total genetic impacts of 0.3-2.1% by considering both marginal associations and genetic interactions with cigarette smoking or alcohol consumption, corresponding to 39.3% and 14.6-26.7% of the total and SNP-based heritability of HBP-S1, respectively.

In chapter V, we conducted two independent GxE studies for quantitative outcomes: 1) a GWIS for testing gene-by-obesity interactions on lipid levels and 2) a GWIS for testing gene-by-lifestyle interactions on BP levels. In the first study, we detected four genetic variants located on *APOA5* and *BUD13* interacting with BMI. The identified variants had strong marginal genetic effects on TG: rs2075291 (p-value=$3.52\text{x}10^{-76}$) and rs651821 (p-value=$2.42\text{x}10^{-140}$) on *APOA5*, rs2000571 (p-value=$9.70\text{x}10^{-25}$) and rs2041967 (p-value=$6.59\text{x}10^{-31}$) on *BUD13*. All the identified SNPs were in LD with rs1558860 located on *BUD13*, which reported in our previous GWISs for the risk of abnormal TG elevation, except for rs2041967 (r^2=0.20). In the second GWIS, on the other hand, we identified a novel genetic variant located on *TSPAN5* interacting with heavy drinking to modify quantitative SBP levels: rs12501917 (p-value=$1.75\text{x}10^{-8}$). We could not detect any gene-by-lifestyle interactions on quantitative DBP levels.

Many human traits or diseases are known to be a consequence of the combined effect of genes, environmental factors, and their interactions. Studies on GxEs hold the key to further insights on human complex traits and the development of better prediction

models for diseases. Our studies on GxEs at a genome-wide scale, so-called GWISs, for Koreans revealed novel genetic loci of dyslipidemia and hypertension interacting with lifestyle risk factors: cigarette smoking, alcohol consumption, and obesity traits. Compared with GWAS-identified loci having marginal effects only, the inclusion of GxE SNPs clearly explained more of the total and genetic variances of dyslipidemia and hypertension. Based on the different allele frequencies between Caucasians and Asians, in addition, Asians experience a higher risk of dyslipidemia, particularly for TG, despite a small increase in obesity traits, such as BMI, WC, or WHR. The newly identified gene-by-obesity and gene-by-lifestyle interactions can be used to classify individuals into higher-risk or lower-risk groups and to personalize health guidelines for managing lipid and BP traits according to an individual's genetic constitution.

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Table 1. Basic characteristics of the participants in each Korean cohort

	Total	Reference Set		Replication Set	
		Ansan Cohort	Ansung Cohort	Urban Cohort	Rural Cohort
Participants	16,014	4,236	3,606	3,436	4,736
Age (Years)	55.2±9.4	50.1±7.7	56.9±8.8	52.7±8.2	60.2±9.3
Sex, Male (%)	7,075 (44.2)	2,136 (50.4)	1,531 (42.5)	1,494 (43.5)	1,914 (40.4)
BMI (kg/m^2)	24.2±3.0	24.5±2.8	24.4±3.2	23.9±2.9	23.9±3.2
WC (cm)	82.9±8.7	80.4±7.9	85.6±8.5	82.2±8.8	83.5±8.8
HC (cm)	93.4±5.9	94.1±4.7	91.0±5.5	95.3±5.8	93.2±6.6
WHR	0.89±0.07	0.85±0.06	0.94±0.06	0.86±0.06	0.90±0.06
Total-C (mmol/L)*	5.07±0.87	5.11±0.81	4.87±0.80	5.13±0.88	5.13±0.94
HDL-C (mmol/L)*	1.23±0.29	1.18±0.24	1.17±0.24	1.42±0.33	1.18±0.29
LDL-C (mmol/L)*	3.11±0.80	3.18±0.74	2.96±0.72	3.08±0.82	3.20±0.85
TG (mmol/L)*	1.57±1.01	1.64±0.96	1.63±0.99	1.37±0.98	1.62±1.08
Remnant-C (mmol/L)*	0.72±0.46	0.75±0.44	0.75±0.45	0.63±0.45	0.74±0.49

LDL-C was calculated using the Friedewald's formula for individuals with TG under 4.52 mmol/L; Remnant-C was determined as the level of Total-C minus HDL-C minus LDL-C. *Plasma levels of lipids were adjusted for age, age^2, and sex. Detailed features stratified by obesity status into subgroups based on BMI, WC, and WHR are presented in Supplemental Table S2 and S3.

Table 2. Novel gene-by-obesity interactive loci modifying the risk of dyslipidemia identified from the meta-analysis of the Korean cohorts

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	
Total-C	BMI	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.81 3.88E-09	0.79 4.26E-10	1.47 7.32E-03	CT1/CT2/EDGxE
	WC	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 4.04E-09	0.76 3.07E-08	1.18 1.62E-02	CT1/CT2/EDGxE
		COL4A3BP	rs7733436	5	74666492	0.48	C/T	0.81 5.38E-09	0.78 1.97E-10	1.27 1.13E-02	CT1/CT2/EDGxE
	WHR	*HMGCR*	rs7702895	5	74612893	0.48	G/A	0.81 7.29E-09	0.72 3.15E-08	1.22 5.40E-03	CT1/CT2/EDGxE
HDL-C	BMI	*LOC101929680/SCN1A*	rs11890028	2	166943277	0.09	G/T	0.96 4.19E-01	0.92 8.78E-02	2.30 2.79E-08	CO
LDL-C	BMI	*LOC101928271*	rs11693076	2	21140033	0.20	C/T	0.75 1.25E-09	0.96 6.54E-01	0.70 6.79E-04	CT1/CT2/EDGxE
	WC	*ANKDD1B*	rs7703282	5	74906963	0.46	A/C	0.77 7.72E-10	0.74 6.12E-11	1.30 2.45E-02	CT1/CT2/EDGxE
	WHR	*ANKDD1B*	rs7703282	5	74906963	0.46	A/C	0.77 9.08E-10	0.70 4.41E-08	1.19 4.57E-02	EDGxE
TG	BMI	*LOC105374079/SLC12A8*	rs77008808	3	124868173	0.06	T/C	0.97 6.37E-01	0.89 9.29E-02	2.70 4.33E-08	CO
		BUD13	rs1558860	11	116607368	0.22	A/C	1.55 5.10E-35	1.76 1.01E-14	0.80 3.27E-03	EDGxE
	WC	*APOA5*	rs651821	11	116662579	0.29	C/T	1.87 1.56E-73	2.01 5.00E-47	0.81 4.06E-04	CT1/CT2/EDGxE
		BUD13	rs918144	11	116633825	0.47	T/C	0.71 4.22E-28	0.66 1.47E-19	1.17 7.75E-03	EDGxE
	WHR	*BUD13*	rs180378	11	116588909	0.32	A/G	1.37 8.00E-22	1.65 6.04E-18	0.76 1.26E-05	DG1/CT1/CT2/EDGxE
		APOA5/ZPR1(ZNF259)	rs2075291	11	116661392	0.08	A/C	1.98 8.80E-42	2.23 4.26E-21	0.82 2.43E-02	CT1/CT2
		APOA5	rs651821	11	116662579	0.29	C/T	1.86 6.82E-73	2.26 8.52E-41	0.74 3.92E-06	DG1/CT1/CT2/EDGxE

Table 2. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	
Remnant-C	BMI	*BUD13*	rs7926828	11	116586423	0.31	C/T	1.35 1.76E-18	1.33 5.07E-16	1.37 4.88E-02	EDGxE
	WC	*BUD13*	rs2075295	11	116628401	0.47	C/T	0.75 1.53E-27	0.73 2.21E-27	1.16 1.16E-02	EDGxE
	WHR	*BUD13*	rs180378	11	116588909	0.32	A/G	1.35 5.63E-26	1.47 1.92E-15	0.84 1.07E-03	EDGxE
		APOA5	rs651821	11	116662579	0.29	C/T	1.82 1.52E-87	1.99 4.07E-41	0.82 1.76E-04	CT1/CT2/EDGxE

The results for each gene-by-obesity interaction were summarized according to the discriminators of obesity traits: BMI, WC, and WHR. More detailed results are presented in Supplemental Table S4.

Table 3. Contributions of gene-by-obesity interactive loci to abnormal lipid profiles

Trait	Heritability (%) (SNP-Based Heritability)	Environment	Gene	Marker	A1/A2	Contribution (%) of Genetic Variants							
						Contribution of GWAS-identified Loci for KOR (Number of SNPs)	Additional Contribution of Gene-by-Obesity Interaction (Allele Frequency in Each Ethnic Group*)						Total Genetic Contribution in KOR population
							KOR	EAS	SAS	EUR	AMR	AFR	
Total-C	35.5 (17.7-24.9)	BMI	*COL4A3BP*	rs7733436	C/T	9.5 (20)	1.2 (0.48)	1.2 (0.49)	1.1 (0.41)	1.2 (0.61)	1.2 (0.54)	0.3 (0.06)	10.7
		WC	*HMGCR*	rs2878417	G/A	8.4 (17)	1.3 (0.48)	1.3 (0.50)	1.2 (0.40)	1.3 (0.58)	1.3 (0.53)	1.3 (0.57)	10.8
			COL4A3BP	rs7733436	C/T		1.1 (0.48)	1.2 (0.49)	1.1 (0.41)	1.2 (0.61)	1.2 (0.54)	0.2 (0.06)	
		WHR	*HMGCR*	rs7702895	G/A	7.2 (15)	1.9 (0.48)	1.9 (0.49)	1.8 (0.40)	1.9 (0.56)	1.9 (0.46)	0.2 (0.03)	9.1
HDL-C	34.8 (18.4-26.2)	BMI	*LOC101929680/SCN1A*	rs11890028	G/T	19.5 (31)	0.3 (0.09)	0.4 (0.13)	0.8 (0.28)	0.8 (0.29)	0.6 (0.21)	0.4 (0.16)	19.8
LDL-C	31.7 (17.2-25.6)	BMI	*LOC101928271*	rs11693076	C/T	5.5 (11)	0.9 (0.20)	0.9 (0.20)	1.0 (0.22)	1.6 (0.46)	1.6 (0.48)	1.7 (0.85)	6.4
		WC	*ANKDD1B*	rs7703282	A/C	6.3 (14)	1.8 (0.46)	1.8 (0.48)	1.7 (0.43)	1.8 (0.62)	1.8 (0.54)	0.4 (0.06)	8.1
		WHR	*ANKDD1B*	rs7703282	A/C	5.6 (12)	2.4 (0.46)	2.4 (0.48)	2.4 (0.43)	2.3 (0.62)	2.4 (0.54)	0.5 (0.06)	8.0
TG	38.3 (18.4-26.4)	BMI	*LOC105374079/SLC12A8*	rs77008808	T/C	48.2 (53)	0.3 (0.06)	0.3 (0.07)	0.2 (0.04)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	52.7
			BUD13	rs1558860	A/C		4.2 (0.22)	4.5 (0.24)	3.8 (0.19)	2.0 (0.09)	2.8 (0.13)	0.2 (0.01)	
		WC	*APOA5*	rs651821	C/T	36.6 (40)	7.4 (0.29)	7.3 (0.29)	5.5 (0.19)	2.6 (0.08)	4.5 (0.15)	4.8 (0.16)	47.1
			BUD13	rs918144	T/C		3.2 (0.47)	3.0 (0.38)	3.2 (0.56)	3.2 (0.48)	3.1 (0.60)	2.9 (0.68)	
		WHR	*BUD13*	rs180378	A/G	39.3 (48)	4.6 (0.32)	4.7 (0.32)	5.4 (0.60)	5.3 (0.43)	5.2 (0.40)	5.4 (0.46)	58.0
			APOA5/ZPR1(ZNF259)	rs2075291	A/C		3.4 (0.08)	1.8 (0.04)	0.5 (0.01)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	
			APOA5	rs651821	C/T		10.7 (0.29)	10.7 (0.29)	7.9 (0.19)	3.8 (0.08)	6.6 (0.15)	6.9 (0.16)	

Table 3. Continued

Trait	Heritability (%) (SNP-Based Heritability)	Environment	Gene	Marker	A1/A2	Contribution (%) of Genetic Variants							
						Contribution of GWAS-identified Loci for KOR (Number of SNPs)	Additional Contribution of Gene-by-Obesity Interaction (Allele Frequency in Each Ethnic Group*)						Total Genetic Contribution in KOR population
							KOR	EAS	SAS	EUR	AMR	AFR	
Remnant-C	48.6 (11.3-14.2)	BMI	*BUD13*	rs7926828	C/T	35.8 (55)	1.3 (0.31)	1.3 (0.32)	1.5 (0.52)	1.0 (0.22)	1.1 (0.25)	1.3 (0.31)	37.0
		WC	*BUD13*	rs2075295	C/T	36.7 (56)	1.8 (0.47)	1.7 (0.38)	1.8 (0.46)	1.4 (0.27)	1.8 (0.44)	1.6 (0.34)	38.5
		WHR	*BUD13*	rs180378	A/G	38.5 (59)	2.4 (0.32)	2.4 (0.32)	2.7 (0.60)	2.7 (0.43)	2.7 (0.40)	2.8 (0.46)	47.8
			APOA5	rs651821	C/T		6.9 (0.29)	6.8 (0.29)	5.1 (0.19)	2.4 (0.08)	4.2 (0.15)	4.5 (0.16)	

Abbreviations for each ethnic group are as follows: Korean (KOR), East Asian (EAS), South Asian (SAS), European (EUR), American (AMR), and African (AFR). *MAFs of each SNP in various ethnic groups were referred to the 1000 Genomes Project database (GRCh37/hg19).

Table 4. Basic characteristics of the participants in each Korean cohort

	Total	Reference Set		Replication Set	
		Ansan Cohort	Ansung Cohort	Urban Cohort	Rural Cohort
Participants	15,954	4,256	3,680	3,319	4,699
Age (Years)	55.1±9.4	50.0±7.6	56.7±8.7	52.5±8.1	60.2±9.3
Sex, Male (%)	7,037 (44.1)	2,154 (50.6)	1,568 (42.6)	1,420 (42.8)	1,895 (40.3)
BMI (kg/m^2)	24.2±3.1	24.5±2.9	24.4±3.3	23.9±2.9	23.9±3.1
WC (cm)	82.9±8.7	80.5±7.9	85.6±8.5	82.1±8.7	83.4±8.7
HC (cm)	93.4±5.9	94.2±4.8	91.0±5.6	95.3±5.8	93.1±6.6
WHR	0.89±0.07	0.85±0.06	0.94±0.06	0.86±0.06	0.90±0.06
SBP (mmHg)*	121.2±14.7	117.6±14.0	126.8±15.1	121.3±13.4	120.0±14.4
DBP (mmHg)*	79.2±9.5	79.1±9.6	83.6±8.7	76.9±9.4	77.3±8.9
MAP (mmHg)*	93.2±10.6	91.9±10.6	98.0±10.3	91.7±10.1	91.5±10.0
PP (mmHg)*	42.0±9.5	38.4±7.9	43.2±9.8	44.4±8.7	42.7±10.2
Mid-BP (mmHg)*	100.2±11.4	98.4±11.4	105.2±11.3	99.1±10.7	98.7±10.9

We defined MAP as the sum of DBP and PP divided by three. PP was determined as the level of SBP minus DBP. Mid-BP was the average of SBP and DBP. *BP-related traits were adjusted for age, age^2, sex, and BMI.

Table 5. Novel gene-by-lifestyle interactive loci modifying the risk of hypertension identified from the meta-analysis of the Korean cohorts

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	
HBP-S1	Ever Smoking	*DCC*	rs9950661	18	50627680	0.34	C/T	0.87 9.85E-08	0.89 1.25E-04	0.90 3.54E-02	CT1/CT2
HBP-S1	Low-Risk Drinking	*BRAP*	rs10774633	12	112096289	0.40	C/T	1.05 3.87E-02	1.04 1.44E-01	1.43 3.71E-10	CO
HBP-S1		*CUX2*	rs10849933	12	111757647	0.32	A/C	1.03 3.39E-01	1.01 7.38E-01	1.45 2.47E-08	CO
HBP-S1		*SH2B3*	rs11065905	12	111887974	0.46	G/A	1.05 1.08E-01	1.03 2.55E-01	1.46 3.84E-08	CO
HBP-S1		*MAPKAPK5*	rs11066065	12	112329287	0.44	C/G	1.06 1.29E-02	1.05 5.53E-02	1.44 1.21E-10	CO
HBP-S1		*HECTD4*	rs11066230	12	112715324	0.39	G/A	1.06 2.83E-02	1.04 9.79E-02	1.39 5.29E-09	CO
HBP-S1		*PTPN11*	rs11066315	12	112895141	0.40	G/A	1.07 6.06E-03	1.06 2.58E-02	1.38 2.19E-08	CO
HBP-S1		*C12orf51 (HECTD4)*	rs12579396	12	112594814	0.39	C/T	1.06 1.58E-02	1.05 6.10E-02	1.39 4.56E-09	CO
HBP-S1		*RPH3A*	rs886476	12	113319471	0.37	G/A	0.91 3.52E-04	0.93 9.03E-03	0.64 1.33E-12	CO/CT2/EDGxE
HBP-S1	Heavy Drinking	*BRAP*	rs10774633	12	112096289	0.40	C/T	1.05 6.06E-02	1.03 2.79E-01	1.42 5.23E-13	CO/EDGxE
HBP-S1		*PTPN11*	rs11066315	12	112895141	0.40	G/A	1.07 1.05E-02	1.05 6.86E-02	1.41 2.82E-12	CO
HBP-S1		*ALDH2*	rs112605264	12	112249140	0.40	A/C	1.05 6.68E-02	1.03 3.00E-01	1.41 5.48E-13	CO
HBP-S1		*MYL2*	rs4766517	12	111359712	0.49	C/G	1.00 9.00E-01	0.97 3.19E-01	1.38 4.63E-10	CO
HBP-S1		*MYL2*	rs4766527	12	111405470	0.43	G/T	0.99 7.13E-01	0.98 3.32E-01	1.33 1.73E-09	CO
HBP-S1		*RPH3A*	rs886476	12	113319471	0.37	G/A	0.92 6.01E-04	0.94 1.51E-02	0.71 1.66E-11	CO
HBP-S1		*CUX2*	rs916683	12	111616207	0.42	C/G	1.06 2.56E-02	1.04 1.39E-01	1.35 6.03E-10	CO

Table 5. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	
HBP-S1	Moderate Drinking	*KLF4*	rs79977578	9	110833870	0.09	G/T	0.97 4.74E-01	1.19 1.63E-03	0.60 7.81E-09	CC/EB
HBP-S1		*CUX2*	rs1265566	12	111716376	0.33	C/T	1.03 2.08E-01	0.98 6.30E-01	1.25 1.70E-10	CO
HBP-S1		*RPH3A*	rs4767019	12	113289070	0.38	G/A	0.93 2.44E-03	0.90 2.41E-04	0.81 2.52E-07	EDGxE
HBP-S1	Binge Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.87 1.21E-04	0.87 2.33E-04	0.37 1.51E-09	CO
HBP-S2	Obesity	*ST5*	rs140343181	11	8763373	0.01	A/G	0.90 3.96E-01	0.79 9.39E-02	4.23 3.75E-08	CO
HBP-S2		*RP11-981P6.1*	rs1689040	12	89978233	0.39	T/C	0.86 2.19E-07	0.85 2.79E-08	1.34 2.29E-02	EDGxE
HBP-S2	Abdominal Obesity Class 1	*ATP2B1*	rs2681472	12	90008959	0.38	G/A	0.85 7.98E-08	0.82 1.32E-06	1.13 2.17E-02	CT1/CT2
HBP-S2	Abdominal Obesity Based on WHR	*MYL2*	rs12229654	12	111414461	0.14	G/T	0.89 8.20E-03	0.80 1.58E-03	1.20 4.53E-02	EDGxE

The results for each gene-by-lifestyle interaction were summarized according to the behavioral traits of cigarette smoking, alcohol consumption, and obesity. Detailed results are presented in Supplemental Table S8.

Table 6. Contributions of gene-by-lifestyle interactive loci to HBP-S1 and HBP-S2

Trait	Heritability (%) (SNP-Based Heritability)	Environment	Gene	Marker	A1/A2	Contribution (%) of Genetic Variants							
						Contribution of GWAS-identified Loci for KOR (Number of SNPs)	Additional Contribution of Gene-by-Lifestyle Interaction (Allele Frequency in Each Ethnic Group*)						Total Genetic Contribution in KOR population
							KOR	EAS	SAS	EUR	AMR	AFR	
HBP-S1	39.3 (14.6-26.7)	Ever Smoking	*DCC*	rs9950661	C/T	6.3 (14)	0.4 (0.34)	0.5 (0.40)	0.4 (0.31)	0.5 (0.53)	0.4 (0.36)	0.5 (0.60)	6.7
HBP-S1		Low-Risk Drinking	*BRAP*	rs10774633	C/T	6.3 (14)	0.2 (0.40)	0.2 (0.42)	0.5 (0.92)	0.5 (1.00)	0.5 (0.89)	0.4 (0.82)	8.2
HBP-S1			*CUX2*	rs10849933	A/C		0.2 (0.32)	0.2 (0.34)	0.5 (0.66)	0.7 (0.83)	0.7 (0.83)	0.5 (0.63)	
HBP-S1			*SH2B3*	rs11065905	G/A		0.2 (0.46)	0.2 (0.50)	0.4 (0.92)	0.4 (1.00)	0.4 (0.88)	0.4 (0.84)	
HBP-S1			*MAPKAPK5*	rs11066065	C/G		0.2 (0.44)	0.2 (0.45)	0.4 (0.98)	0.4 (1.00)	0.4 (0.86)	0.4 (1.00)	
HBP-S1			*HECTD4*	rs11066230	G/A		0.2 (0.39)	0.2 (0.43)	0.3 (0.92)	0.4 (1.00)	0.3 (0.86)	0.3 (0.95)	
HBP-S1			*PTPN11*	rs11066315	G/A		0.2 (0.40)	0.2 (0.42)	0.3 (0.92)	0.3 (1.00)	0.3 (0.86)	0.3 (0.94)	
HBP-S1			*C12orf51*	rs12579396	C/T		0.2 (0.39)	0.2 (0.43)	0.3 (0.92)	0.3 (1.00)	0.3 (0.86)	0.3 (0.95)	
HBP-S1			*RPH3A*	rs886476	G/A		0.6 (0.37)	0.6 (0.39)	0.9 (0.56)	0.9 (0.58)	0.6 (0.39)	0.4 (0.29)	
HBP-S1		Heavy Drinking	*BRAP*	rs10774633	C/T	6.3 (14)	0.2 (0.40)	0.2 (0.42)	0.5 (0.92)	0.6 (1.00)	0.5 (0.89)	0.5 (0.82)	8.2
HBP-S1			*PTPN11*	rs11066315	G/A		0.2 (0.40)	0.2 (0.42)	0.4 (0.92)	0.4 (1.00)	0.4 (0.86)	0.4 (0.94)	
HBP-S1			*ALDH2*	rs112605264	A/C		0.2 (0.40)	0.2 (0.43)	0.5 (0.92)	0.6 (1.00)	0.5 (0.85)	0.5 (0.88)	
HBP-S1			*MYL2*	rs4766517	C/G		0.6 (0.49)	0.6 (0.51)	0.9 (0.74)	0.7 (0.59)	0.9 (0.71)	1.0 (0.81)	
HBP-S1			*MYL2*	rs4766527	G/T		0.2 (0.43)	0.2 (0.48)	0.3 (0.67)	0.2 (0.56)	0.3 (0.69)	0.2 (0.61)	
HBP-S1			*RPH3A*	rs886476	G/A		0.4 (0.37)	0.4 (0.39)	0.6 (0.56)	0.6 (0.58)	0.4 (0.39)	0.3 (0.29)	
HBP-S1			*CUX2*	rs916683	C/G		0.2 (0.42)	0.2 (0.45)	0.3 (0.69)	0.4 (0.83)	0.4 (0.80)	0.1 (0.27)	

Table 6. Continued

Trait	Heritability (%) (SNP-Based Heritability)	Environment	Gene	Marker	A1/A2	Contribution (%) of Genetic Variants							
						Contribution of GWAS-identified Loci for KOR (Number of SNPs)	Additional Contribution of Gene-by-Lifestyle Interaction (Allele Frequency in Each Ethnic Group*)						Total Genetic Contribution in KOR population
							KOR	EAS	SAS	EUR	AMR	AFR	
HBP-S1	39.3 (14.6-26.7)	Moderate Drinking	*KLF4*	rs79977578	G/T	6.3 (14)	1.4 (0.09)	1.4 (0.09)	1.9 (0.12)	0.0 (0.00)	0.5 (0.03)	0.0 (0.00)	8.5
HBP-S1			*CUX2*	rs1265566	C/T		0.2 (0.33)	0.2 (0.33)	0.3 (0.51)	0.2 (0.32)	0.3 (0.52)	0.2 (0.32)	
HBP-S1			*RPH3A*	rs4767019	G/A		0.5 (0.38)	0.6 (0.40)	0.7 (0.56)	0.7 (0.58)	0.6 (0.40)	0.6 (0.47)	
HBP-S1		Binge Drinking	*OAS3*	rs2072134	A/G	6.7 (15)	0.3 (0.11)	0.3 (0.12)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	7.0
HBP-S2	29.0 (16.7-25.9)	Obesity	*ST5*	rs140343181	A/G	5.7 (11)	0.2 (0.01)	0.1 (0.01)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	6.9
HBP-S2			*RP11-981P6.1*	rs1689040	T/C		1.0 (0.39)	1.0 (0.36)	1.1 (0.43)	1.0 (0.38)	0.9 (0.30)	1.1 (0.42)	
HBP-S2		Abdominal Obesity Class 1	*ATP2B1*	rs2681472	G/A	3.7 (7)	1.2 (0.38)	1.1 (0.32)	1.2 (0.34)	0.7 (0.15)	0.5 (0.11)	0.4 (0.09)	4.9
HBP-S2		Abdominal Obesity Based on WHR	*MYL2*	rs12229654	G/T	4.6 (9)	*1.1 (0.14)	1.2 (0.16)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	5.6

Abbreviations for each ethnic group are as follows: Korean (KOR), East Asian (EAS), South Asian (SAS), European (EUR), American (AMR), and African (AFR). *MAFs of each SNP in various ethnic groups were referred to the 1000 Genomes Project database (GRCh37/hg19).

Table 7. Basic characteristics of the participants in each Korean cohort for quantitative GxE analyses

a. Basic characteristics of the participants in each Korean cohort for gene-by-obesity interaction study on quantitative lipid levels

	Total	Reference Set		Replication Set	
		Ansan Cohort	Ansung Cohort	Urban Cohort	Rural Cohort
Participants	15,754	4,141	3,533	3,353	4,727
Age (Years)	55.2±9.5	50.0±7.6	56.8±8.8	52.6±8.2	60.2±9.3
Sex, Male (%)	6,973 (44.3)	2,096 (50.6)	1,508 (42.7)	1,461 (43.6)	1,908 (40.4)
BMI (kg/m^2)	24.2±3.0	24.5±2.8	24.4±3.2	23.9±2.9	23.9±3.2
WC (cm)	82.8±8.7	80.4±7.9	85.5±8.4	82.2±8.7	83.5±8.8
HC (cm)	93.4±5.9	94.1±4.7	90.9±5.5	95.3±5.8	93.2±6.6
WHR	0.89±0.07	0.85±0.06	0.94±0.06	0.86±0.06	0.90±0.06
Total-C (mmol/L)*	5.06±0.87	5.09±0.80	4.86±0.78	5.13±0.88	5.13±0.94
HDL-C (mmol/L)*	1.23±0.29	1.18±0.24	1.17±0.24	1.42±0.33	1.18±0.29
LDL-C (mmol/L)*	3.11±0.80	3.17±0.73	2.95±0.72	3.08±0.81	3.20±0.85
TG (mmol/L)*	1.57±1.00	1.63±0.94	1.62±0.95	1.36±0.97	1.62±1.08
Remnant-C (mmol/L)*	0.72±0.46	0.74±0.43	0.74±0.44	0.62±0.45	0.74±0.49

Table 7. Continued

b. Basic characteristics of the participants in each Korean cohort for gene-by-lifestyle interaction study on quantitative BP levels

	Total	Reference Set		Replication Set	
		Ansan Cohort	Ansung Cohort	Urban Cohort	Rural Cohort
Participants	15,954	4,256	3,680	3,319	4,699
Age (Years)	55.1±9.4	50.0±7.6	56.7±8.7	52.5±8.1	60.2±9.3
Sex, Male (%)	7,037 (44.1)	2,154 (50.6)	1,568 (42.6)	1,420 (42.8)	1,895 (40.3)
BMI (kg/m^2)	24.2±3.1	24.5±2.9	24.4±3.3	23.9±2.9	23.9±3.1
WC (cm)	82.9±8.7	80.5±7.9	85.6±8.5	82.1±8.7	83.4±8.7
HC (cm)	93.4±5.9	94.2±4.8	91.0±5.6	95.3±5.8	93.1±6.6
WHR	0.89±0.07	0.85±0.06	0.94±0.06	0.86±0.06	0.90±0.06
SBP (mmHg)*	121.2±14.7	117.6±14.0	126.8±15.1	121.3±13.4	120.0±14.4
DBP (mmHg)*	79.2±9.5	79.1±9.6	83.6±8.7	76.9±9.4	77.3±8.9
MAP (mmHg)*	93.2±10.6	91.9±10.6	98.0±10.3	91.7±10.1	91.5±10.0
PP (mmHg)*	42.0±9.5	38.4±7.9	43.2±9.8	44.4±8.7	42.7±10.2
Mid-BP (mmHg)*	100.2±11.4	98.4±11.4	105.2±11.3	99.1±10.7	98.7±10.9

Table 8. Comparison of the identified gene-by-obesity interactions on dyslipidemia defined in dichotomous and quantitative TG scales

Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWIS for Dyslipidemia			GWIS for Quantitative TG		
							GWAS	GxE Interaction		GWAS	GxE Interaction	
							OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)
BMI	*LOC105374079/SLC12A8*	rs77008808	3	124868173	0.06	T/C	0.97 6.37E-01	0.89 9.29E-02	2.70 **4.33E-08***	-0.01 3.45E-01	-0.02 1.44E-01	0.16 7.54E-03
	BUD13	rs1558860	11	116607368	0.22	A/C	1.55 5.10E-35	1.76 1.01E-14	0.80 **3.27E-03***	0.10 3.76E-61	0.09 4.41E-18	0.02 1.46E-01
	BUD13	rs2000571	11	116585533	0.30	A/G	1.33 1.48E-12	1.19 5.05E-02	1.13 2.15E-01	0.07 9.70E-25	0.04 9.85E-05	0.04 **1.09E-02***
	BUD13	rs2041967	11	116645149	0.42	G/A	0.72 1.83E-24	0.67 7.61E-09	1.11 2.03E-01	-0.06 6.59E-31	-0.04 5.86E-06	-0.03 **3.13E-03***
	APOA5	rs2075291	11	116661392	0.08	A/C	1.99 3.34E-42	1.90 4.99E-10	1.06 6.07E-01	0.18 3.52E-76	0.15 4.32E-19	0.05 **1.00E-02***
	APOA5	rs651821	11	116662579	0.29	C/T	1.87 9.71E-73	2.03 3.47E-22	0.90 2.05E-01	0.15 2.42E-140	0.12 9.15E-37	0.04 **2.12E-03***

We conducted additional analyses for testing gene-by-obesity interactions using quantitative TG levels as outcome variables. For this analysis, we transformed quantitative TG levels into a logarithmic scale; it is known that some non-normal distribution would generate false interactions. We identified novel GxE variants using the reference set consisting of the Ansan and Ansung cohorts; all the results were confirmed using the replication set composed of the urban and rural cohorts. *The *p*-value of significance represents the novel gene-by-obesity interactions.

Table 9. Comparison of the identified gene-by-lifestyle interactions on hypertension defined in dichotomous and quantitative SBP scales

Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWIS for Hypertension			GWIS for Quantitative SBP		
							GWAS	GxE Interaction		GWAS	GxE Interaction	
							OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)
Low-Risk Drinking	*BRAP*	rs10774633	12	112096289	0.40	C/T	1.05 3.87E-02	1.04 1.44E-01	1.43 **3.71E-10***	0.32 7.89E-02	0.31 9.99E-02	0.10 8.85E-01
	CUX2	rs10849933	12	111757647	0.32	A/C	1.03 3.39E-01	1.01 7.38E-01	1.45 **2.47E-08***	0.59 7.81E-03	0.47 4.14E-02	1.49 6.75E-02
	SH2B3	rs11065905	12	111887974	0.46	G/A	1.05 1.08E-01	1.03 2.55E-01	1.46 **3.84E-08***	0.06 7.56E-01	0.07 7.12E-01	-0.19 7.92E-01
	MAPKAPK5	rs11066065	12	112329287	0.44	C/G	1.06 1.29E-02	1.05 5.53E-02	1.44 **1.21E-10***	0.43 1.63E-02	0.42 2.47E-02	0.14 8.34E-01
	HECTD4	rs11066230	12	112715324	0.39	G/A	1.06 2.83E-02	1.04 9.79E-02	1.39 **5.29E-09***	0.40 2.48E-02	0.41 3.00E-02	-0.05 9.42E-01
	PTPN11	rs11066315	12	112895141	0.40	G/A	1.07 6.06E-03	1.06 2.58E-02	1.38 **2.19E-08***	0.42 2.16E-02	0.44 2.26E-02	-0.19 7.70E-01
	C12orf51	rs12579396	12	112594814	0.39	C/T	1.06 1.58E-02	1.05 6.10E-02	1.39 **4.56E-09***	0.40 2.70E-02	0.41 3.10E-02	-0.08 8.98E-01
	RPH3A	rs886476	12	113319471	0.37	G/A	0.91 3.52E-04	0.93 9.03E-03	0.64 **1.33E-12***	-0.62 8.02E-04	-0.51 7.93E-03	-1.53 3.28E-02

We carried out additional analyses for detecting gene-by-lifestyle interactions, especially genetic interactions with alcohol consumption, using quantitative SBP and DBP levels as outcome variables. We identified novel GxE loci using the reference set consisting of the Ansan and Ansung cohorts; all the results were confirmed using the replication set composed of the urban and rural cohorts. *The *p*-value of significance represents the novel gene-by-lifestyle interactions.

Table 9. Continued

Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWIS for Hypertension			GWIS for Quantitative SBP		
							GWAS	GxE Interaction		GWAS	GxE Interaction	
							OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)
Heavy Drinking	*TSPAN5*	rs12501917	4	99686361	0.24	A/G	1.02 5.80E-01	0.99 7.17E-01	1.28 7.27E-03	0.02 9.14E-01	-0.39 7.50E-02	3.67 **1.75E-08***
	BRAP	rs10774633	12	112096289	0.40	C/T	1.05 6.06E-02	1.03 2.79E-01	1.42 **5.23E-13***	0.27 1.32E-01	0.23 2.39E-01	0.38 4.95E-01
	PTPN11	rs11066315	12	112895141	0.40	G/A	1.07 1.05E-02	1.05 6.86E-02	1.41 **2.82E-12***	0.37 4.11E-02	0.35 6.97E-02	0.15 7.84E-01
	ALDH2	rs112605264	12	112249140	0.40	A/C	1.05 6.68E-02	1.03 3.00E-01	1.41 **5.48E-13***	0.27 1.37E-01	0.22 2.57E-01	0.42 4.50E-01
	MYL2	rs4766517	12	111359712	0.49	C/G	1.00 9.00E-01	0.97 3.19E-01	1.38 **4.63E-10***	0.15 4.62E-01	0.00 9.89E-01	1.32 3.97E-02
	MYL2	rs4766527	12	111405470	0.43	G/T	0.99 7.13E-01	0.98 3.32E-01	1.33 **1.73E-09***	-0.12 4.87E-01	-0.21 2.75E-01	0.67 2.11E-01
	RPH3A	rs886476	12	113319471	0.37	G/A	0.92 6.01E-04	0.94 1.51E-02	0.71 **1.66E-11***	-0.58 1.52E-03	-0.51 8.93E-03	-0.66 2.59E-01
	CUX2	rs916683	12	111616207	0.42	C/G	1.06 2.56E-02	1.04 1.39E-01	1.35 **6.03E-10***	0.51 4.68E-03	0.47 1.57E-02	0.38 4.98E-01

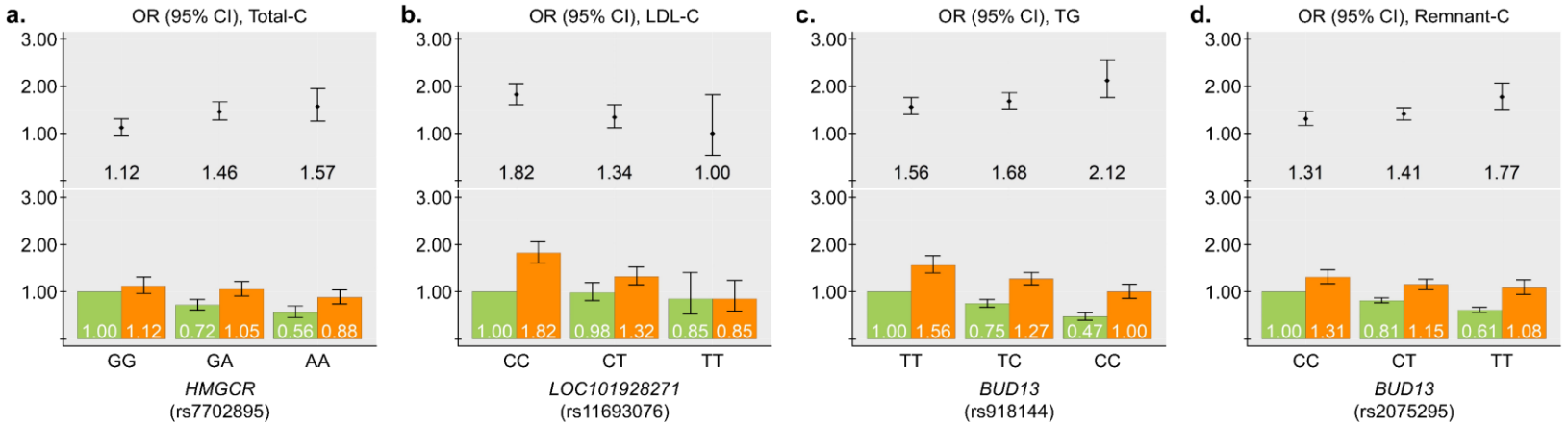


Figure 1. Gene-by-obesity interactive effects on the risk of dyslipidemia. The bar plots on the lower side of each graph describe the OR as the ratio of the probability of dyslipidemia occurring in each exposed group (G≠0 or E≠0) to the probability in a non-exposed group (G=0 and E=0). The upper plots, on the other hand, show multiplicative effects of obesity traits for each genetic group. The figures describe the estimated dyslipidemia OR due to interactions between (a) *HMGCR* and abdominal obesity based on WHR, (b) *LOC101928271* and overweight class 1, (c) *BUD13* and abdominal obesity class 1, (d) *BUD13* and abdominal obesity class 2, (e) *LOC101929680/SCN1A* and obesity, (f) *APOA5* and abdominal obesity based on WHR, (g) *APOA5* and abdominal obesity based on WHR. Further details are presented in Supplemental Table S6.

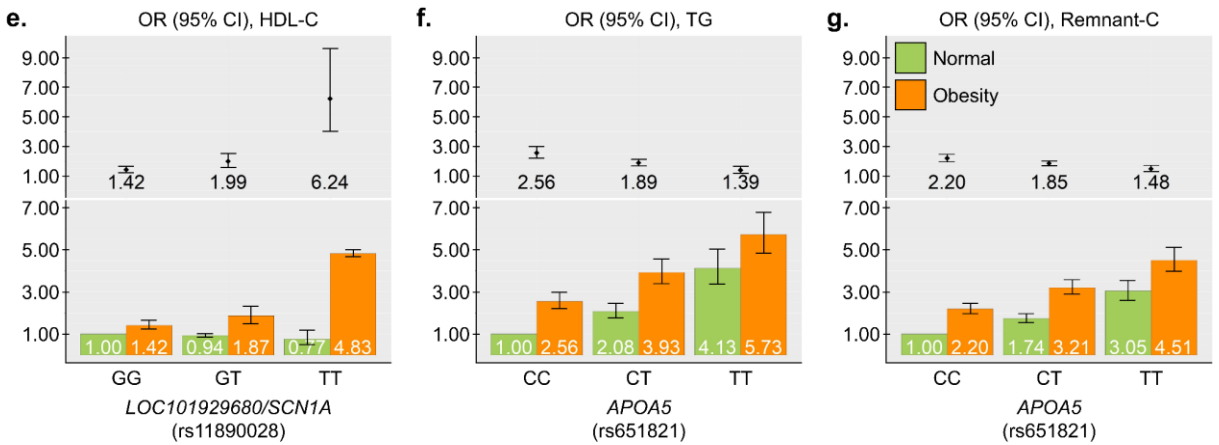


Figure 1. Continued

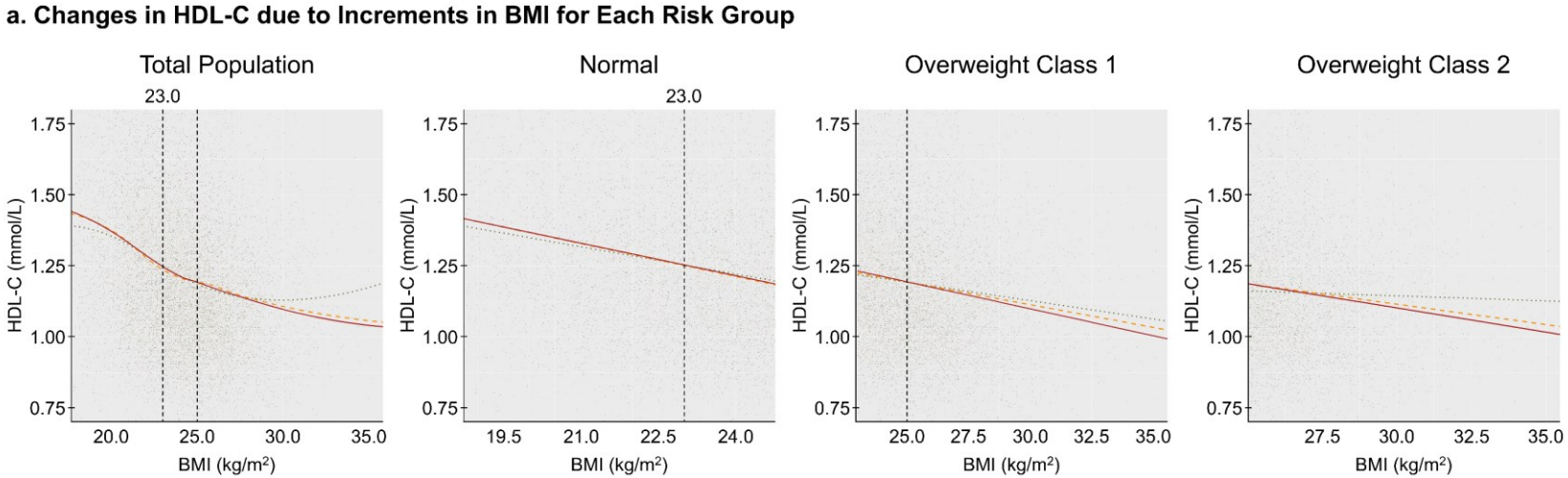


Figure 2. Changes in plasma lipid levels due to the increments in BMI for each risk group. The study population was classified into three groups by the number of risk alleles on gene-by-obesity interactive markers: the low-risk group (individuals with no risk alleles), the high-risk group (individuals with at least one risk allele), and the higher-risk group (the upper 50% of individuals belong to the high-risk group). Figures above describe the trends of plasma lipid levels due to an increment of 1 kg/m^2 in BMI for each group. (a) The differences in the decrement of HDL-C for each genetic group were far clearer in the obese group than in the group with normal BMI. (b) The differences in the increment of TG for each risk group were far clearer in the obese group than in the normal BMI group; details are presented in Supplemental Table S7.

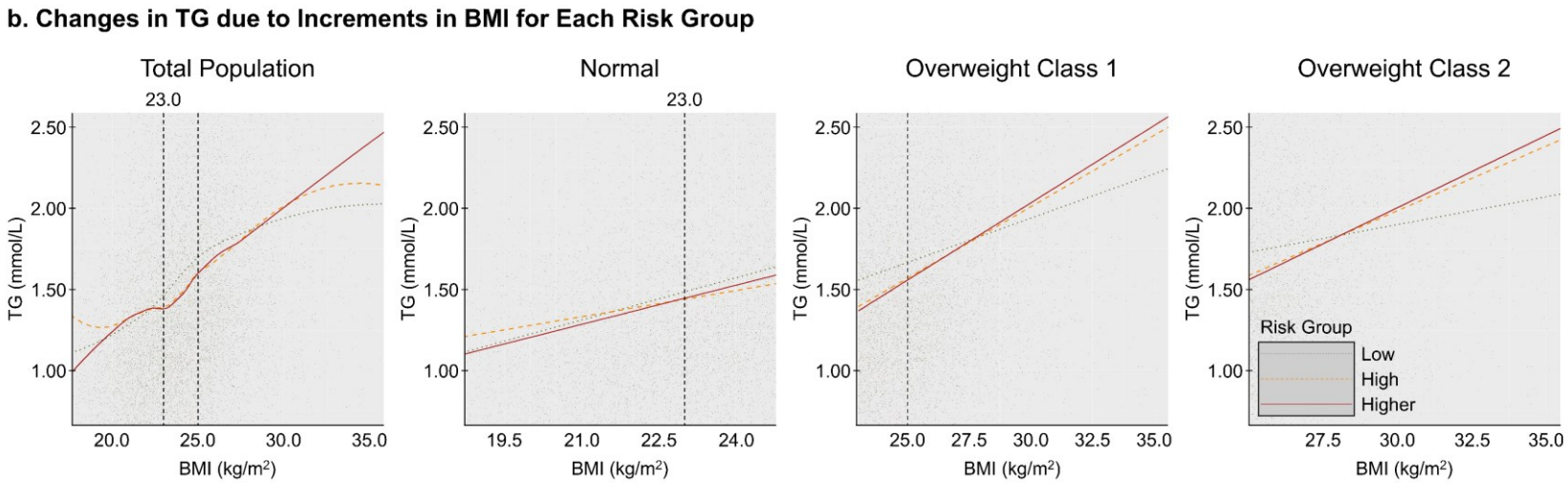


Figure 2. Continued

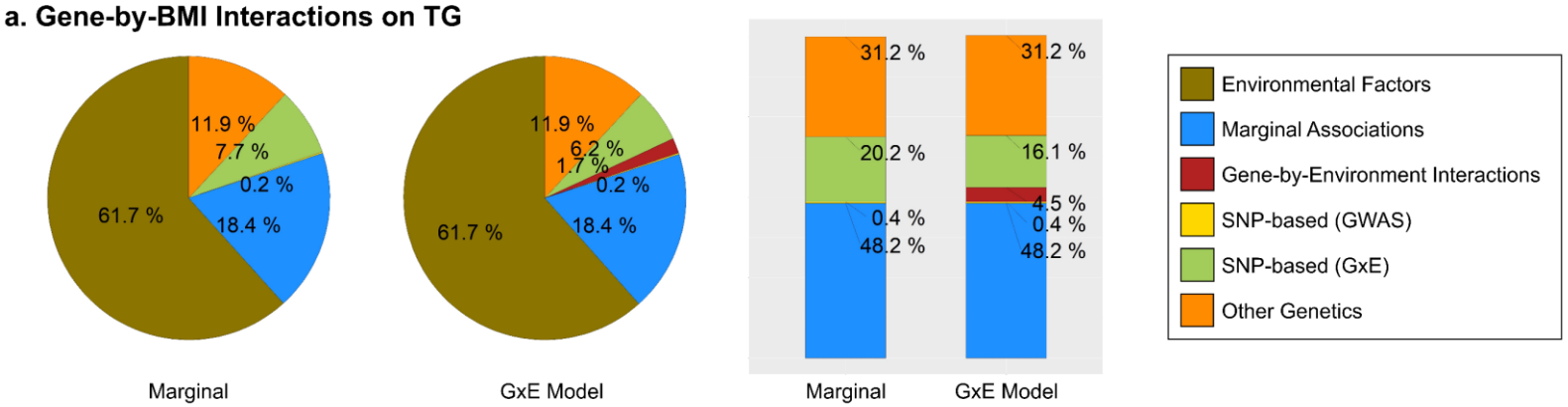


Figure 3. Contributions of marginal associations and gene-by-obesity interactions to the risk of dyslipidemia. The pie plots describe the proportion of phenotypic variation attributable to the overall genetic variation (total heritability), genetic markers assayed by SNP arrays (SNP-based heritability), and the combined set of both GWAS-identified and novel GxE variants. The bar plots, on the other hand, show the proportion of genetic variation explained by marginal genetic and gene-by-obesity interactive effects. Figures (a) to (c) describe the genetic contributions to abnormal TG attributable to the interaction between genes and obesity traits classified by (a) BMI, (b) WC, and (c) WHR. Figure (d) describes the contributions to abnormal Remnant-C attributable to the interaction between genes and obesity traits classified by WHR; further details are described in Table 3.

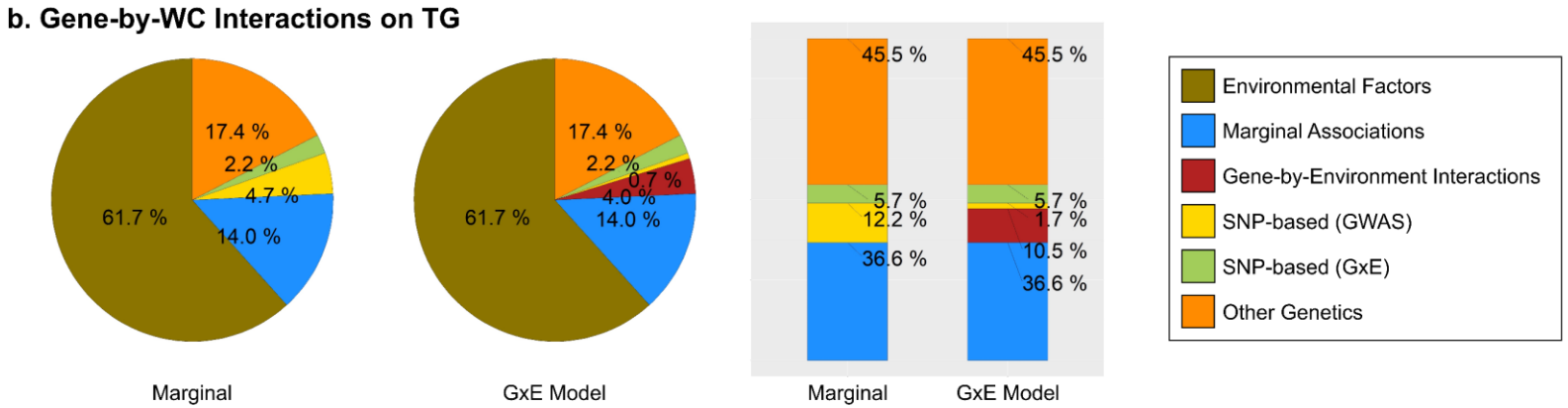


Figure 3. Continued

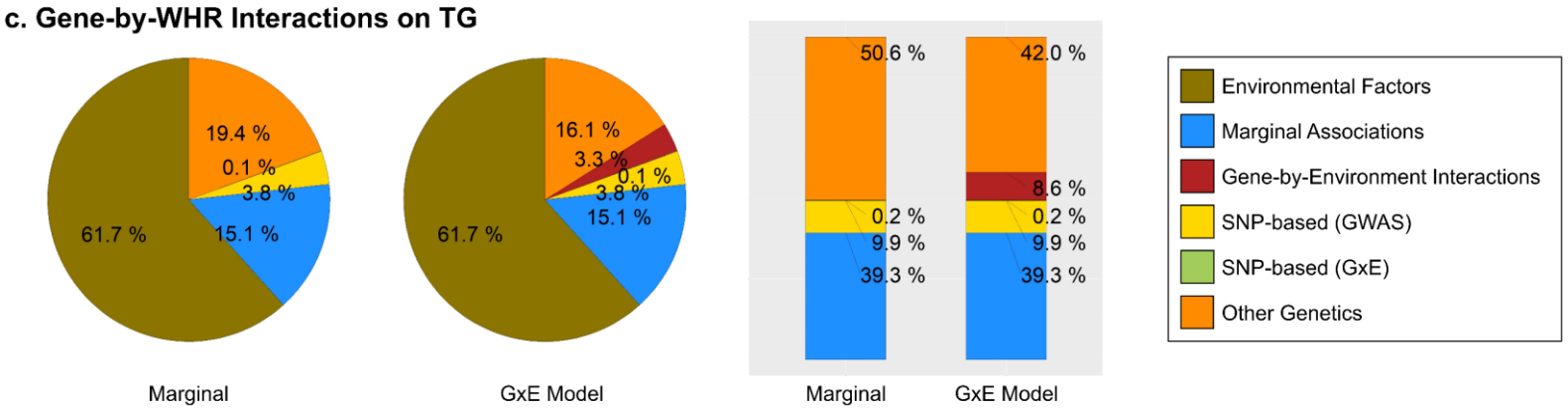


Figure 3. Continued

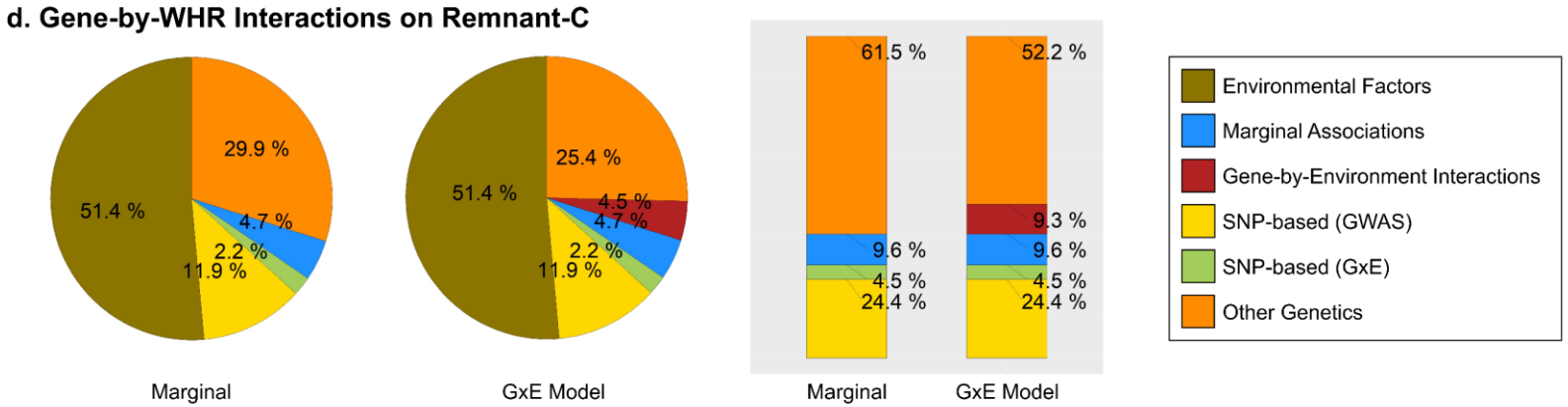


Figure 3. Continued

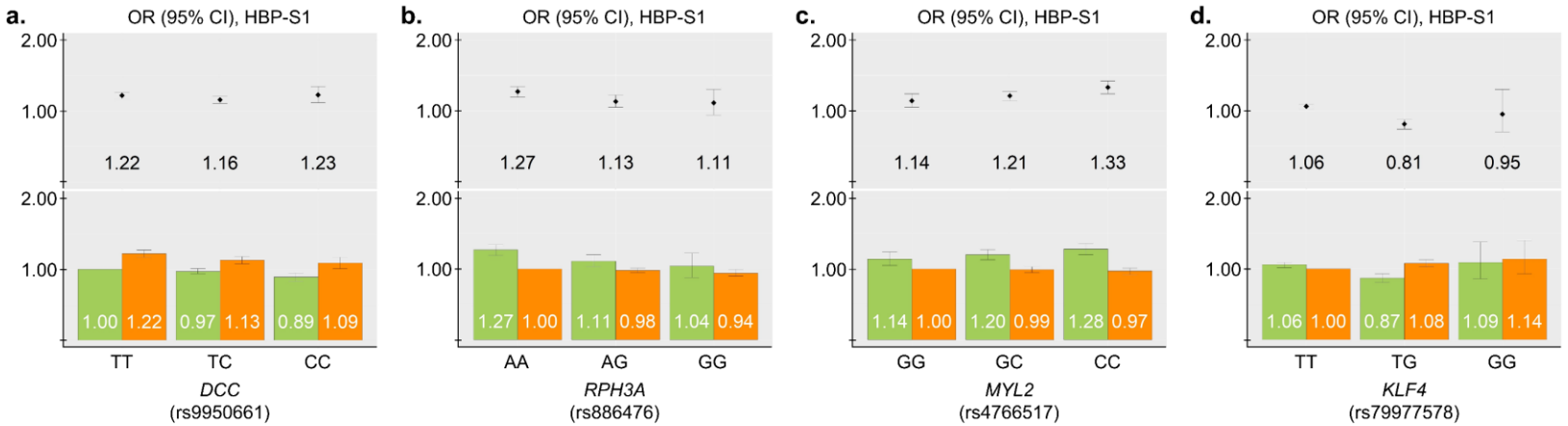


Figure 4. Gene-by-Lifestyle interactive effects on the risk of hypertension. The bar plots on the lower side of each graph show ORs as the ratio of hypertension probability occurring in each exposed group (G≠0 or E≠0) to the probability in a non-exposed group (G=0 and E=0). The upper plots, on the other hand, describe multiplicative effects of lifestyle factors for each genetic group. The figure above shows estimated ORs of HBP-S1 or HBP-S2 attributable to the interplay between (a) *DCC* and ever smoking, (b) *RPH3A* and low-risk drinking, (c) *MYL2* and heavy drinking, (d) *KLF4* and moderate drinking, (e) *RP11-981P6.1* and obesity, (f) *ATP2B1* and abdominal obesity class 1, (g) *MYL2* and abdominal obesity based on WHR. Further details are provided in Supplemental Table S10.

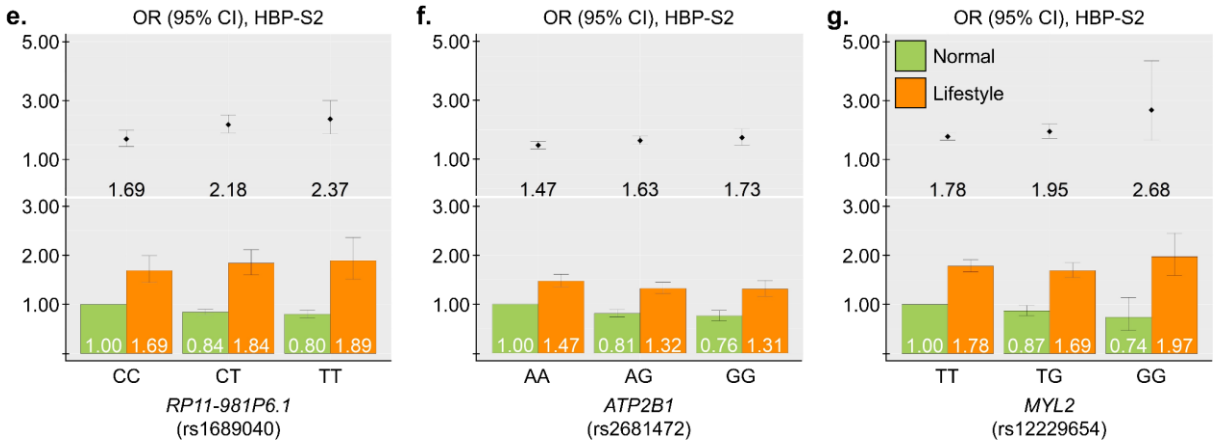


Figure 4. Continued

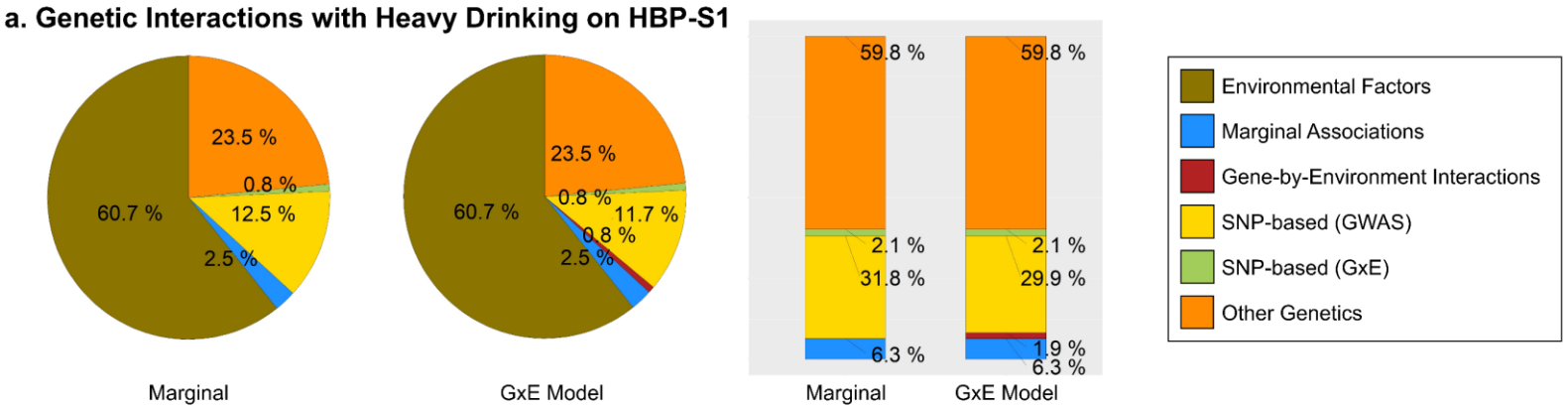
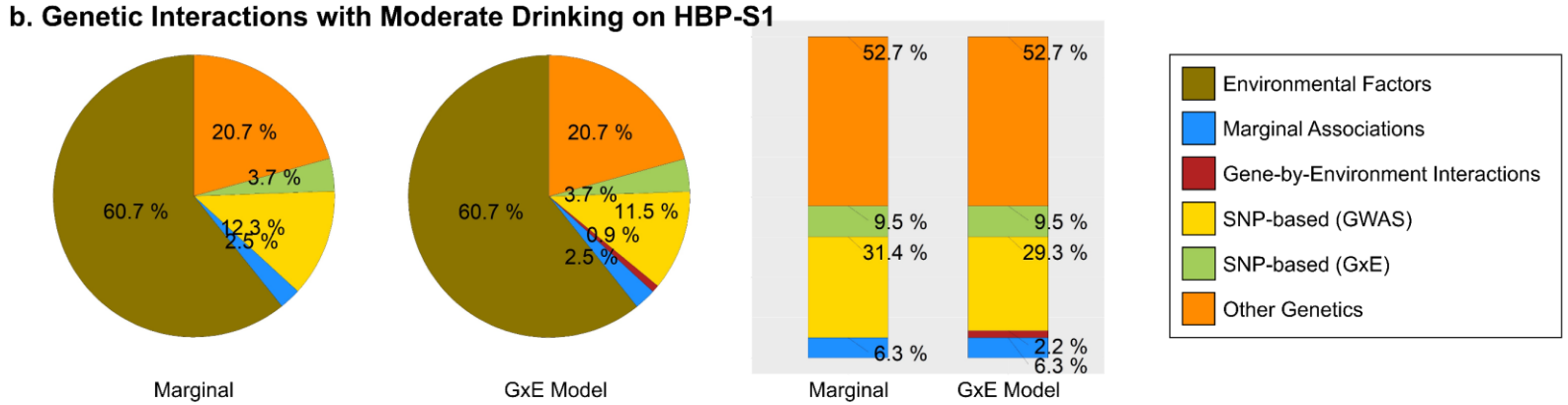


Figure 5. Contributions of marginal associations and gene-by-lifestyle interactions to the risk of hypertension. The pie plots describe the proportion of phenotypic variation attributable to the overall genetic variation (total heritability), genetic markers assayed by SNP arrays (SNP-based heritability), and the combined set of both GWAS-identified and novel GxE variants. The bar plots, on the other hand, show the proportion of genetic variation explained by marginal genetic and gene-by-lifestyle interactive effects. Figure (a) and (b) describe the genetic contributions to HBP-S1 attributable to the interaction between genes and alcohol consumption. Figure (c) and (d) show the contributions to HBP-S2 due to the interaction between genes and obesity traits; further details are described in Table 6.



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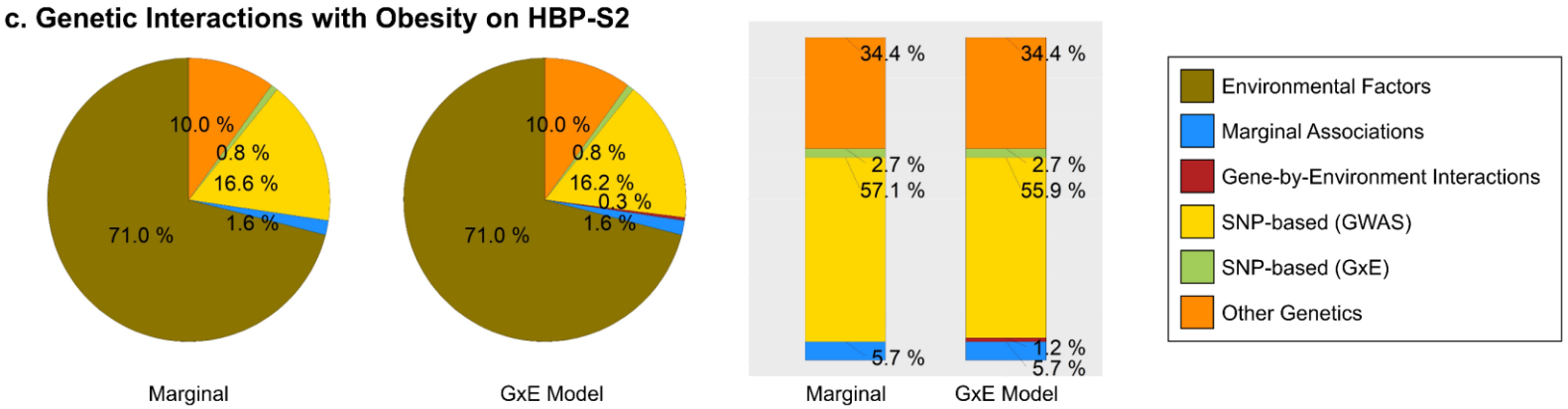


Figure 5. Continued

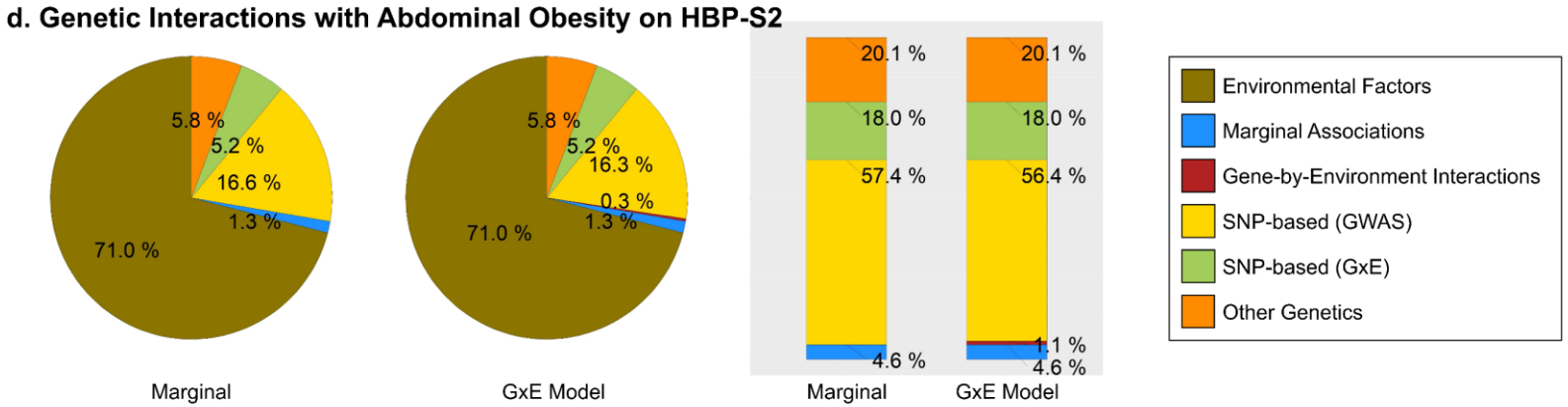


Figure 5. Continued

Supplemental Table S1. Definitions of outcome variables and environmental factors

a. Clinical thresholds for outcome variables

Outcome Variable	Trait	Definition
Dyslipidemia	Abnormal Total-C	Total-C≥6.21 mmol/L
	Abnormal HDL-C	HDL-C≤1.03 mmol/L (for males) or 1.29 mmol/L (for females), the lowest quintile (20%)*
	Abnormal LDL-C	LDL-C≥4.14 mmol/L
	Abnormal TG	TG≥2.26 mmol/L
	Abnormal Remnant-C	the highest quintile (20%)
Hypertension	HBP-S1	130≤SBP<140 mmHg or 80≤DBP<90 mmHg
	HBP-S2	SBP≥140 mmHg or DBP≥90 mmHg

*For HDL-C, we used the lowest quintile as a cut-off point because the clinical cut-off points (HDL-C≤1.03 mmol/L for males or 1.29 mmol/L for females) resulted in too many dyslipidemia cases (46.8%) in our study populations.

Supplemental Table S1. Continued

b. Clinical thresholds for environmental factors

Environmental Factor	Trait	Definition
Alcohol Consumption	Moderate Drinking	Alcohol Intake≤28.0 g/day (for males) or 14.0 g/day (for females)
	Low-Risk Drinking	28.0<Alcohol Intake≤56.0 g/day (for males) or 14.0<Alcohol Intake≤28.0 g/day (for females)
	Heavy Drinking	Alcohol Intake>56.0 g/day (for males) or 42.0 g/day (for females)
	Binge Drinking	Alcohol Intake≥70.0 g/day (for males) or 56.0 g/day (for females)
Obesity	Underweight	BMI<18.5 kg/m^2
	Overweight Class 1	BMI≥23.0 kg/m^2
	Overweight Class 2	BMI≥25.0 kg/m^2
	Obesity	BMI≥30.0 kg/m^2
Abdominal Obesity	Abdominal Obesity Class 1	WC>90 cm (for males) or 80 cm (for females)
	Abdominal Obesity Class 2	WC>102 cm (for males) or 88 cm (for females)
	Abdominal Obesity Based on WHR	WHR>0.90 (for males) or 0.85 (for females)

Supplemental Table S2. Basic characteristics of the participants in the combined Korean cohort

	Total	Obesity Based on BMI					Abdominal Obesity (WC)			Abdominal Obesity (WHR)	
		BMI<18.5	18.5-23.0	23.0-25.0	25.0-30.0	30.0≤BMI	Normal	Class 1	Class 2	Normal	Obese
Participants (%)	16,014	360 (2.2)	5,349 (33.4)	4,265 (26.6)	5,451 (34.0)	589 (3.7)	9,615 (60.0)	4,285 (26.8)	2,114 (13.2)	7,029 (43.9)	8,985 (56.1)
Age (Years)	55.2±9.4	61.2±10.6	55.7±10.1	54.6±9.1	54.8±8.9	55.0±8.6	54.0±9.6	56.2±9.0	58.8±8.4	52.3±9.1	57.4±9.1
Sex, Male (%)	7,075 (44.2)	193 (53.6)	2,365 (44.2)	1,894 (44.4)	2,470 (45.3)	153 (26.0)	5,417 (56.3)	1,575 (36.8)	83 (3.9)	3,394 (48.3)	3,681 (41.0)
BMI (kg/m^2)	24.2±3.0	17.6±0.9	21.3±1.2	24.0±0.6	26.7±1.3	31.8±1.8	22.8±2.3	25.6±2.3	27.8±2.9	22.9±2.7	25.2±3.0
WC (cm)	82.9±8.7	68.8±5.6	76.4±6.2	82.6±5.6	88.7±6.2	98.1±7.7	78.2±6.6	87.7±5.5	94.4±5.4	77.0±6.8	87.4±7.1
HC (cm)	93.4±5.9	83.5±4.6	89.3±4.4	93.3±3.9	96.9±4.4	104.1±5.8	91.2±5.0	95.9±5.2	98.4±6.3	92.9±5.7	93.8±6.1
WHR	0.89±0.07	0.82±0.06	0.86±0.07	0.89±0.06	0.92±0.06	0.94±0.07	0.86±0.06	0.92±0.05	0.96±0.06	0.83±0.05	0.93±0.05
Total-C (mmol/L)	5.07±0.88	4.61±0.85	4.92±0.86	5.10±0.88	5.19±0.88	5.31±0.91	4.97±0.86	5.15±0.89	5.31±0.90	4.97±0.85	5.14±0.90
Adjusted Total-C	5.07±0.87	4.63±0.84	4.93±0.85	5.10±0.87	5.18±0.87	5.27±0.91	5.01±0.86	5.12±0.88	5.21±0.90	5.01±0.84	5.11±0.89
HDL-C (mmol/L)	1.23±0.30	1.38±0.36	1.31±0.32	1.22±0.28	1.16±0.26	1.16±0.26	1.26±0.31	1.18±0.27	1.17±0.25	1.29±0.32	1.18±0.27
Adjusted HDL-C	1.23±0.29	1.40±0.35	1.31±0.31	1.22±0.28	1.16±0.26	1.14±0.26	1.27±0.31	1.18±0.27	1.15±0.25	1.29±0.31	1.18±0.27
LDL-C (mmol/L)	3.11±0.81	2.71±0.79	3.00±0.78	3.15±0.81	3.21±0.82	3.27±0.84	3.04±0.79	3.18±0.83	3.33±0.82	3.06±0.78	3.16±0.83
Adjusted LDL-C	3.11±0.80	2.72±0.76	3.01±0.76	3.15±0.80	3.21±0.82	3.22±0.83	3.08±0.79	3.15±0.82	3.20±0.82	**3.09±0.78**	**3.13±0.82***
TG (mmol/L)	1.57±1.03	1.14±0.70	1.33±0.86	1.58±1.04	1.80±1.09	1.95±1.34	1.47±0.99	1.73±1.10	1.75±0.97	1.36±0.87	1.74±1.11
Adjusted TG	1.57±1.01	1.12±0.71	1.33±0.85	1.58±1.02	1.79±1.07	2.00±1.32	1.43±0.97	1.75±1.07	1.86±0.96	1.36±0.86	1.74±1.09
Remnant-C (mmol/L)	0.72±0.47	0.52±0.32	0.61±0.39	0.73±0.48	0.82±0.50	0.89±0.61	0.67±0.45	0.79±0.50	0.80±0.44	0.62±0.40	0.80±0.51
Adjusted Remnant-C	0.72±0.46	0.51±0.32	0.61±0.39	0.72±0.47	0.82±0.49	0.91±0.60	0.66±0.45	0.80±0.49	0.85±0.44	0.62±0.39	0.80±0.50

*** *p*-value=6.25x10^{-3}**

Differences between the means for obesity subgroups stratified by BMI, WC, and WHR were examined by the *F*-test (ANOVA) for continuous values and the chi-square test for categorical values; all results were significant (p-value<0.005). Plasma levels of each lipid were adjusted for age, age^2, and sex. LDL-C was calculated using the Friedewald's formula for individuals with TG under 4.52 mmol/L; Remnant-C was defined as the level of Total-C minus HDL-C minus LDL-C.

Supplemental Table S3. Basic characteristics of the participants in each Korean cohort

a. Basic characteristics of the participants in the Ansan cohort

	Total	Obesity Based on BMI					Abdominal Obesity (WC)			Abdominal Obesity (WHR)	
		BMI<18.5	18.5-23.0	23.0-25.0	25.0-30.0	30.0≤BMI	Normal	Class 1	Class 2	Normal	Obese
Participants (%)	4,236	42 (1.0)	1,219 (28.8)	1,223 (28.9)	1,601 (37.8)	151 (3.6)	3,218 (76.0)	818 (19.3)	200 (4.7)	2,799 (66.1)	1,437 (33.9)
Age (Years)	50.1±7.7	51.4±10.0	49.3±7.3	49.9±7.6	50.7±7.8	51.9±8.5	49.2±7.2	52.4±8.1	55.7±9.1	48.6±6.7	53.1±8.4
Sex, Male (%)	2,136 (50.4)	23 (54.8)	573 (47.0)	637 (52.1)	856 (53.5)	47 (31.1)	1,810 (56.2)	316 (38.6)	10 (5.0)	1,347 (48.1)	789 (54.9)
BMI (kg/m^2)	24.5±2.8	17.8±0.7	21.4±1.1	24.0±0.6	26.7±1.3	31.7±1.9	23.6±2.2	27.0±2.0	29.7±3.0	23.6±2.5	26.3±2.6
WC (cm)	80.4±7.9	65.2±3.8	73.4±5.4	79.6±4.9	85.5±5.5	94.1±6.4	77.9±6.6	87.3±5.5	93.3±4.8	76.9±6.3	87.4±5.7
HC (cm)	94.1±4.7	84.6±2.8	90.0±3.1	93.5±2.7	97.1±3.2	104.2±4.5	92.8±3.9	97.7±3.9	101.8±5.5	93.3±4.4	95.7±4.9
WHR	0.85±0.06	0.77±0.04	0.82±0.06	0.85±0.05	0.88±0.05	0.90±0.05	0.84±0.06	0.89±0.05	0.92±0.04	0.82±0.05	0.91±0.04
Total-C (mmol/L)	5.11±0.82	4.56±0.87	4.93±0.77	5.14±0.81	5.22±0.82	5.33±0.97	5.05±0.80	5.25±0.81	5.47±1.00	5.02±0.80	5.29±0.83
Adjusted Total-C	5.11±0.81	4.57±0.86	4.95±0.75	5.14±0.80	5.20±0.81	5.32±0.95	5.07±0.79	5.21±0.80	5.41±0.98	5.05±0.79	5.23±0.83
HDL-C (mmol/L)	1.18±0.24	1.38±0.31	1.27±0.25	1.18±0.23	1.12±0.22	1.12±0.22	1.20±0.25	1.12±0.21	1.15±0.24	1.22±0.25	1.12±0.21
Adjusted HDL-C	1.18±0.24	1.39±0.31	1.26±0.25	1.18±0.22	1.13±0.22	1.10±0.22	1.20±0.24	1.12±0.21	1.11±0.24	1.21±0.25	1.12±0.21
LDL-C (mmol/L)	3.18±0.75	2.69±0.73	3.06±0.70	3.22±0.75	3.25±0.77	3.22±0.81	3.14±0.74	3.26±0.77	3.42±0.85	3.14±0.72	3.25±0.79
Adjusted LDL-C	3.18±0.74	2.70±0.72	3.07±0.68	3.22±0.74	3.24±0.76	3.19±0.80	3.16±0.73	3.22±0.76	3.33±0.83	**3.16±0.71**	**3.21±0.79***
TG (mmol/L)	1.64±0.98	1.06±0.30	1.34±0.79	1.61±0.92	1.85±1.04	2.18±1.50	1.55±0.92	1.88±1.14	1.98±1.09	1.45±0.81	2.00±1.18
Adjusted TG	1.64±0.96	1.03±0.43	1.36±0.78	1.61±0.90	1.83±1.01	2.24±1.48	1.54±0.89	1.91±1.09	2.11±1.09	1.48±0.79	1.95±1.16
Remnant-C (mmol/L)	0.75±0.45	0.48±0.14	0.61±0.36	0.74±0.42	0.85±0.48	1.00±0.68	0.71±0.42	0.86±0.52	0.91±0.50	0.67±0.37	0.91±0.54
Adjusted Remnant-C	0.75±0.44	0.47±0.20	0.62±0.36	0.74±0.41	0.84±0.46	1.03±0.68	0.71±0.41	0.87±0.50	0.97±0.50	0.68±0.36	0.89±0.53

*** *p*-value=2.54x10^{-2}**

Differences between the means for obesity subgroups stratified by BMI, WC, and WHR were examined by the *F*-test (ANOVA) for continuous values and the chi-square test for categorical values; all results were significant (p-value<0.005). Plasma levels of each lipid were adjusted for age, age^2, and sex. LDL-C was calculated using the Friedewald's formula for individuals with TG under 4.52 mmol/L; Remnant-C was defined as the level of Total-C minus HDL-C minus LDL-C.

Supplemental Table S3. Continued

b. Basic characteristics of the participants in the Ansung cohort

	Total	Obesity Based on BMI					Abdominal Obesity (WC)			Abdominal Obesity (WHR)	
		BMI<18.5	18.5-23.0	23.0-25.0	25.0-30.0	30.0≤BMI	Normal	Class 1	Class 2	Normal	Obese
Participants (%)	3,606	97 (2.7)	1,119 (31.0)	902 (25.0)	1,301 (36.1)	187 (5.2)	1,642 (45.5)	1,074 (29.8)	890 (24.7)	534 (14.8)	3,072 (85.2)
Age (Years)	56.9±8.8	61.4±8.2	58.0±9.2	56.5±8.7	56.0±8.4	55.7±8.3	56.4±9.2	56.0±8.7	58.7±7.9	54.8±9.8	57.2±8.6
Sex, Male (%)	1,531 (42.5)	65 (67.0)	582 (52.0)	370 (41.0)	474 (36.4)	40 (21.4)	1,139 (69.4)	371 (34.5)	21 (2.4)	357 (66.9)	1,174 (38.2)
BMI (kg/m^2)	24.4±3.2	17.5±0.8	21.3±1.2	24.0±0.6	26.8±1.3	31.7±1.7	22.2±2.3	25.2±2.2	27.6±2.7	21.3±2.4	24.9±3.0
WC (cm)	85.6±8.5	69.5±4.5	78.4±4.9	84.8±4.6	91.2±5.2	100.8±6.2	79.3±6.0	87.6±5.4	94.7±5.5	75.0±5.5	87.4±7.5
HC (cm)	91.0±5.5	80.4±3.2	86.7±3.4	90.5±3.1	94.3±3.6	101.3±4.3	87.7±4.3	92.3±4.3	95.4±4.9	87.7±5.2	91.5±5.3
WHR	0.94±0.06	0.86±0.05	0.90±0.05	0.94±0.05	0.97±0.05	1.00±0.05	0.90±0.05	0.95±0.04	0.99±0.04	0.86±0.03	0.95±0.05
Total-C (mmol/L)	4.87±0.82	4.30±0.75	4.69±0.74	4.88±0.87	5.04±0.80	5.13±0.75	4.66±0.78	4.94±0.81	5.19±0.78	4.50±0.69	4.94±0.82
Adjusted Total-C	4.87±0.80	4.36±0.74	4.72±0.72	4.88±0.85	5.02±0.78	5.06±0.77	4.76±0.78	4.92±0.80	5.04±0.78	4.62±0.70	4.92±0.80
HDL-C (mmol/L)	1.17±0.24	1.29±0.31	1.24±0.25	1.17±0.24	1.11±0.21	1.12±0.22	1.21±0.26	1.13±0.22	1.13±0.21	1.25±0.27	1.15±0.23
Adjusted HDL-C	1.17±0.24	1.29±0.31	1.24±0.25	1.17±0.24	1.11±0.21	1.12±0.21	1.22±0.26	1.13±0.22	1.13±0.21	1.26±0.27	1.15±0.23
LDL-C (mmol/L)	2.96±0.75	2.47±0.66	2.82±0.71	2.96±0.77	3.09±0.74	3.13±0.79	2.77±0.73	3.01±0.75	3.24±0.70	2.67±0.65	3.01±0.76
Adjusted LDL-C	2.96±0.72	2.55±0.64	2.86±0.68	2.96±0.74	3.07±0.72	3.05±0.78	2.88±0.72	2.99±0.74	3.06±0.69	2.81±0.65	2.99±0.73
TG (mmol/L)	1.63±1.00	1.18±0.45	1.38±0.75	1.64±1.05	1.84±1.00	1.91±1.60	1.49±0.97	1.72±1.07	1.77±0.91	1.25±0.55	1.70±1.04
Adjusted TG	1.63±0.99	1.14±0.45	1.37±0.74	1.64±1.04	1.85±0.99	1.95±1.57	1.43±0.96	1.74±1.04	1.86±0.90	1.20±0.54	1.71±1.03
Remnant-C (mmol/L)	0.75±0.46	0.54±0.21	0.63±0.34	0.75±0.48	0.84±0.46	0.87±0.73	0.68±0.45	0.79±0.49	0.81±0.42	0.57±0.25	0.78±0.48
Adjusted Remnant-C	0.75±0.45	0.52±0.21	0.63±0.34	0.75±0.48	0.85±0.45	0.89±0.72	0.66±0.44	0.80±0.48	0.85±0.41	0.55±0.25	0.78±0.47

Supplemental Table S3. Continued

c. Basic characteristics of the participants in the urban cohort

	Total	Obesity Based on BMI					Abdominal Obesity (WC)			Abdominal Obesity (WHR)	
		BMI<18.5	18.5-23.0	23.0-25.0	25.0-30.0	30.0≤BMI	Normal	Class 1	Class 2	Normal	Obese
Participants (%)	3,436	65 (1.9)	1,285 (37.4)	946 (27.5)	1,047 (30.5)	93 (2.7)	2,238 (65.1)	934 (27.2)	262 (7.7)	2,027 (59.0)	1,409 (41.0)
Age (Years)	52.7±8.2	52.6±9.3	51.8±8.2	52.8±8.1	53.6±8.2	54.5±8.0	51.9±8.1	54.0±8.2	55.3±8.0	51.4±7.8	54.7±8.3
Sex, Male (%)	1,494 (43.5)	26 (40.0)	453 (35.3)	440 (46.5)	539 (51.5)	36 (38.7)	1,066 (47.6)	404 (43.3)	24 (9.1)	**858 (42.3)**	**636 (45.1)***
BMI (kg/m^2)	23.9±2.9	17.6±0.7	21.4±1.1	24.0±0.6	26.6±1.2	31.8±1.8	22.6±2.2	25.7±2.1	28.2±3.0	22.9±2.5	25.3±2.8
WC (cm)	82.2±8.8	67.7±5.8	76.1±6.4	82.7±5.6	88.9±6.3	98.5±6.6	78.1±6.8	88.7±5.8	94.7±5.7	78.0±7.3	88.3±7.0
HC (cm)	95.3±5.8	86.5±4.7	91.5±4.3	95.6±3.8	99.3±4.4	107.3±6.0	93.0±4.7	98.9±4.6	102.6±5.9	94.5±5.5	96.6±6.0
WHR	0.86±0.06	0.78±0.06	0.83±0.06	0.86±0.05	0.89±0.05	0.92±0.06	0.84±0.06	0.90±0.05	0.92±0.06	0.83±0.05	0.91±0.04
Total-C (mmol/L)	5.13±0.89	4.83±0.78	5.03±0.88	5.14±0.86	5.22±0.91	5.50±0.94	5.06±0.87	5.22±0.90	5.32±0.99	5.06±0.89	5.22±0.89
Adjusted Total-C	5.13±0.88	4.86±0.76	5.04±0.85	5.13±0.85	5.21±0.92	5.45±0.94	5.08±0.86	5.20±0.89	5.24±0.99	5.08±0.86	5.19±0.89
HDL-C (mmol/L)	1.42±0.34	1.66±0.44	1.52±0.36	1.39±0.32	1.32±0.30	1.34±0.33	1.47±0.35	1.33±0.31	1.34±0.30	1.47±0.35	1.34±0.32
Adjusted HDL-C	1.42±0.33	1.65±0.42	1.50±0.35	1.40±0.31	1.33±0.29	1.34±0.33	1.47±0.34	1.33±0.30	1.29±0.30	1.47±0.34	1.35±0.31
LDL-C (mmol/L)	3.08±0.83	2.69±0.78	2.98±0.80	3.10±0.84	3.17±0.84	3.36±0.87	3.02±0.81	3.15±0.84	3.31±0.88	3.01±0.82	3.17±0.83
Adjusted LDL-C	3.08±0.82	2.71±0.74	2.99±0.77	3.10±0.83	3.16±0.84	3.31±0.87	3.04±0.80	3.13±0.83	3.22±0.88	3.03±0.81	3.14±0.83
TG (mmol/L)	1.37±1.00	1.06±0.95	1.14±0.78	1.41±1.13	1.61±1.06	1.74±0.98	1.27±0.98	1.60±1.08	1.47±0.81	1.25±1.00	1.54±0.99
Adjusted TG	1.37±0.98	1.09±0.92	1.18±0.78	1.40±1.11	1.57±1.03	1.75±0.93	1.25±0.95	1.60±1.04	1.61±0.80	1.26±0.97	1.53±0.97
Remnant-C (mmol/L)	0.63±0.46	0.48±0.44	0.52±0.36	0.65±0.52	0.74±0.48	0.80±0.45	0.58±0.45	0.73±0.49	0.67±0.37	0.57±0.46	0.71±0.45
Adjusted Remnant-C	0.63±0.45	0.50±0.42	0.54±0.36	0.64±0.51	0.72±0.47	0.80±0.43	0.57±0.43	0.73±0.48	0.74±0.37	0.58±0.44	0.70±0.45

*** *p*-value=1.10x10^{-1}**

Supplemental Table S3. Continued

d. Basic characteristics of the participants in the rural cohort

	Total	Obesity Based on BMI					Abdominal Obesity (WC)			Abdominal Obesity (WHR)	
		BMI<18.5	18.5-23.0	23.0-25.0	25.0-30.0	30.0≤BMI	Normal	Class 1	Class 2	Normal	Obese
Participants (%)	4,736	156 (3.3)	1,726 (36.4)	1,194 (25.2)	1,502 (31.7)	158 (3.3)	2,517 (53.1)	1,459 (30.8)	760 (16.0)	1,669 (35.2)	3,067 (64.8)
Age (Years)	60.2±9.3	67.2±7.9	61.6±9.8	59.3±9.0	58.9±8.7	57.5±8.5	**60.3±9.8**	**59.8±9.0**	**60.9±8.3***	58.9±10.0	61.0±8.8
Sex, Male (%)	1,914 (40.4)	79 (50.6)	757 (43.9)	447 (37.4)	601 (40.0)	30 (19.0)	1,402 (55.7)	484 (33.2)	28 (3.7)	832 (49.9)	1,082 (35.3)
BMI (kg/m^2)	23.9±3.2	17.5±0.9	21.3±1.2	24.0±0.6	26.8±1.3	32.1±1.9	22.2±2.4	25.1±2.3	27.4±3.0	22.3±2.9	24.8±3.0
WC (cm)	83.5±8.8	69.8±6.2	77.6±6.3	83.9±5.5	89.7±6.1	98.4±9.3	77.9±6.7	87.5±5.4	94.2±5.2	76.7±7.1	87.1±7.3
HC (cm)	93.2±6.6	83.9±4.7	89.0±5.0	93.5±4.4	97.4±4.9	105.6±6.9	89.9±5.4	95.6±5.1	99.5±6.3	92.0±6.8	93.8±6.4
WHR	0.90±0.06	0.83±0.06	0.87±0.06	0.90±0.05	0.92±0.06	0.93±0.08	0.87±0.06	0.92±0.05	0.95±0.05	0.83±0.04	0.93±0.05
Total-C (mmol/L)	5.13±0.96	4.73±0.89	4.98±0.95	5.19±0.93	5.25±0.96	5.41±0.98	4.99±0.94	5.22±0.95	5.40±0.95	4.95±0.90	5.23±0.98
Adjusted Total-C	5.13±0.94	4.77±0.86	5.00±0.93	5.18±0.91	5.25±0.95	5.34±0.98	5.05±0.93	5.19±0.94	5.26±0.95	5.00±0.88	5.20±0.96
HDL-C (mmol/L)	1.18±0.29	1.32±0.31	1.23±0.30	1.17±0.28	1.12±0.26	1.13±0.26	1.20±0.30	1.15±0.27	1.17±0.26	1.22±0.30	1.16±0.28
Adjusted HDL-C	1.18±0.29	1.32±0.31	1.24±0.30	1.17±0.27	1.12±0.26	1.12±0.26	1.21±0.30	1.15±0.27	1.16±0.26	1.23±0.30	1.16±0.27
LDL-C (mmol/L)	3.20±0.88	2.88±0.85	3.10±0.84	3.26±0.85	3.29±0.92	3.41±0.89	3.10±0.84	3.27±0.90	3.43±0.91	3.10±0.83	3.26±0.90
Adjusted LDL-C	3.20±0.85	2.90±0.81	3.11±0.81	3.25±0.83	3.29±0.90	3.34±0.90	3.17±0.81	3.24±0.88	3.27±0.91	3.15±0.80	3.23±0.88
TG (mmol/L)	1.62±1.09	1.17±0.78	1.43±0.99	1.65±1.06	1.83±1.20	1.89±0.95	1.51±1.08	1.74±1.10	1.74±1.03	1.36±0.87	1.76±1.16
Adjusted TG	1.62±1.08	1.18±0.78	1.43±0.99	1.65±1.04	1.82±1.19	1.93±0.94	1.48±1.07	1.75±1.08	1.83±1.02	1.35±0.86	1.77±1.15
Remnant-C (mmol/L)	0.74±0.50	0.54±0.36	0.65±0.45	0.75±0.48	0.84±0.55	0.87±0.44	0.69±0.50	0.80±0.51	0.80±0.47	0.62±0.40	0.80±0.53
Adjusted Remnant-C	0.74±0.49	0.54±0.36	0.65±0.45	0.76±0.47	0.84±0.54	0.88±0.43	0.68±0.49	0.80±0.50	0.84±0.47	0.62±0.39	0.81±0.53

*** *p*-value=2.91x10^{-2}**

Supplemental Table S3. Continued

e. Basic characteristics of the participants in the Healthy Twin Study

	Total	Obesity Based on BMI					Abdominal Obesity (WC)			Abdominal Obesity (WHR)	
		BMI<18.5	18.5-23.0	23.0-25.0	25.0-30.0	30.0≤BMI	Normal	Class 1	Class 2	Normal	Obese
Participants (%)	3,125	81 (2.6)	1,360 (43.5)	724 (23.2)	869 (27.8)	91 (2.9)	2,127 (68.1)	764 (24.4)	234 (7.5)	1,979 (63.3)	1,146 (36.7)
Age (Years)	44.1±13.3	37.1±13.5	41.5±12.4	45.7±13.5	47.8±13.4	42.8±13.4	41.5±12.3	48.9±13.4	52.5±14.6	39.8±11.4	51.7±13.1
Sex, Male (%)	1,259 (40.3)	21 (25.9)	374 (27.5)	350 (48.3)	474 (54.5)	40 (44.0)	931 (43.8)	304 (39.8)	24 (10.3)	**766 (38.7)**	**493 (43.0)***
BMI (kg/m^2)	23.6±3.2	17.7±0.6	21.1±1.2	24.0±0.6	26.8±1.3	32.5±2.3	22.2±2.3	25.8±2.2	29.0±3.2	22.5±2.6	25.6±3.1
WC (cm)	80.7±9.0	66.4±4.8	74.5±5.5	82.1±5.1	88.7±5.7	100.2±7.4	76.7±6.9	87.6±5.7	95.0±6.8	76.5±7.1	88.0±7.2
HC (cm)	94.8±5.7	86.5±3.2	91.4±3.7	95.3±3.5	99.1±4.3	108.7±5.1	92.8±4.6	98.0±4.8	102.7±6.3	94.0±5.3	96.2±6.1
WHR	0.85±0.07	0.77±0.05	0.82±0.06	0.86±0.05	0.90±0.06	0.92±0.05	0.83±0.06	0.89±0.05	0.93±0.05	0.81±0.05	0.91±0.05
Total-C (mmol/L)	4.90±0.85	4.55±0.79	4.73±0.81	4.93±0.82	5.14±0.87	5.15±0.89	4.79±0.83	5.08±0.83	5.32±0.89	4.77±0.82	5.13±0.85
Adjusted Total-C	4.90±0.82	4.70±0.77	4.78±0.78	4.90±0.81	5.08±0.86	5.17±0.89	4.82±0.80	5.01±0.82	5.25±0.88	4.83±0.80	5.02±0.85
HDL-C (mmol/L)	1.31±0.31	1.48±0.31	1.39±0.31	1.28±0.29	1.20±0.27	1.14±0.28	1.35±0.30	1.23±0.30	1.21±0.28	1.36±0.30	1.22±0.30
Adjusted HDL-C	1.31±0.29	1.43±0.31	1.37±0.30	1.30±0.28	1.23±0.26	1.14±0.27	1.35±0.29	1.24±0.28	1.19±0.28	1.34±0.29	1.25±0.29
LDL-C (mmol/L)	2.87±0.76	2.46±0.66	2.70±0.70	2.91±0.74	3.13±0.77	3.18±0.86	2.77±0.74	3.05±0.71	3.29±0.85	2.75±0.74	3.09±0.75
Adjusted LDL-C	2.87±0.73	2.61±0.64	2.75±0.68	2.88±0.72	3.06±0.77	3.20±0.87	2.80±0.71	2.98±0.70	3.23±0.85	2.81±0.72	2.98±0.75
TG (mmol/L)	1.30±0.88	0.91±0.40	1.03±0.54	1.36±0.94	1.64±0.95	1.99±1.88	1.16±0.76	1.57±1.07	1.65±0.84	1.12±0.73	1.60±1.02
Adjusted TG	1.30±0.84	1.05±0.38	1.11±0.53	1.31±0.92	1.54±0.92	1.99±1.83	1.16±0.72	1.54±1.03	1.73±0.81	1.16±0.69	1.53±1.00
Remnant-C (mmol/L)	0.71±0.34	0.61±0.26	0.64±0.29	0.73±0.33	0.82±0.38	0.83±0.51	0.67±0.31	0.80±0.38	0.82±0.39	0.66±0.30	0.82±0.39
Adjusted Remnant-C	0.71±0.33	0.66±0.27	0.66±0.28	0.72±0.33	0.79±0.37	0.83±0.51	0.68±0.30	0.78±0.38	0.82±0.39	0.67±0.29	0.79±0.39

*** *p*-value=1.98x10^{-2}**

Supplemental Table S4. Gene-by-obesity interactive loci of dyslipidemia obtained from the meta-analysis of the cohorts (before LD clumping)

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
Total-C	Overweight Class 2	*HMGCR*	rs11957260	5	74608732	0.48	C/T	0.81 5.13E-09	0.77 3.95E-08	1.16 3.15E-02	5.13E-09	3.32E-02	5.00E-02	CT1/CT2
Total-C	Overweight Class 2	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 3.90E-09	0.77 5.17E-08	1.15 3.99E-02	3.90E-09	4.33E-02	5.00E-02	CT1/CT2
Total-C	Overweight Class 2	*HMGCR*	rs6892023	5	74611574	0.48	G/T	0.81 5.50E-09	0.77 4.63E-08	1.15 3.31E-02	5.50E-09	3.52E-02	5.00E-02	CT1/CT2
Total-C	Overweight Class 2	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.81 3.80E-09	0.76 3.14E-08	1.15 4.49E-02	3.80E-09	4.54E-02	5.00E-02	CT1/CT2
Total-C	Obesity	*HMGCR*	rs11957260	5	74608732	0.48	C/T	0.81 6.29E-09	0.80 8.46E-10	1.44 1.07E-02	6.29E-09	1.17E-02	5.00E-02	CT1/CT2 EDGxE
Total-C	Obesity	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 4.84E-09	0.80 6.49E-10	1.44 1.02E-02	4.84E-09	1.14E-02	5.00E-02	CT1/CT2 EDGxE
Total-C	Obesity	*HMGCR*	rs4703667	5	74613906	0.48	G/C	0.81 4.76E-09	0.80 7.16E-10	1.43 1.20E-02	4.76E-09	1.38E-02	5.00E-02	CT1/CT2 EDGxE
Total-C	Obesity	*COL4A3BP*	rs4704220	5	74757556	0.48	G/A	0.81 7.91E-09	0.80 8.57E-10	1.48 6.84E-03	7.91E-09	7.33E-03	1.25E-02	CT1/CT2
Total-C	Obesity	*COL4A3BP*	rs6873472	5	74768347	0.48	C/A	0.81 8.39E-09	0.80 9.12E-10	1.48 6.84E-03	8.39E-09	7.34E-03	1.25E-02	CT1/CT2
Total-C	Obesity	*HMGCR*	rs6892023	5	74611574	0.48	G/T	0.81 6.68E-09	0.80 9.43E-10	1.44 1.08E-02	6.68E-09	1.21E-02	5.00E-02	CT1/CT2 EDGxE
Total-C	Obesity	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.81 3.88E-09	0.79 4.26E-10	1.47 7.32E-03	3.88E-09	7.90E-03	5.00E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Class 1	*HMGCR*	rs11957260	5	74608732	0.48	C/T	0.81 5.54E-09	0.76 4.76E-08	1.17 2.20E-02	5.54E-09	2.26E-02	5.00E-02	CT1/CT2
Total-C	Abdominal Obesity Class 1	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 4.04E-09	0.76 3.07E-08	1.18 1.62E-02	4.04E-09	1.70E-02	5.00E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Class 1	*HMGCR*	rs4703667	5	74613906	0.48	G/C	0.81 3.99E-09	0.76 6.07E-08	1.16 2.49E-02	3.99E-09	2.62E-02	5.00E-02	CT1/CT2
Total-C	Abdominal Obesity Class 1	*HMGCR*	rs7702895	5	74612893	0.48	G/A	0.81 5.77E-09	0.76 5.87E-08	1.17 1.99E-02	5.77E-09	2.13E-02	5.00E-02	CT1/CT2
Total-C	Abdominal Obesity Class 1	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.81 3.62E-09	0.76 4.45E-08	1.16 2.70E-02	3.62E-09	2.73E-02	5.00E-02	CT1/CT2
Total-C	Abdominal Obesity Class 2	*HMGCR*	rs11957260	5	74608732	0.48	C/T	0.82 8.89E-09	0.78 3.29E-10	1.26 1.15E-02	8.89E-09	1.15E-02	1.25E-02	EDGxE

Supplemental Table S4. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
Total-C	Abdominal Obesity Class 2	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 6.77E-09	0.78 2.47E-10	1.26 1.13E-02	5.05E-08	1.13E-02	1.25E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Class 2	*HMGCR*	rs4703667	5	74613906	0.48	G/C	0.81 6.46E-09	0.78 3.20E-10	1.24 1.41E-02	6.46E-09	1.41E-02	5.00E-02	CT1/CT2
Total-C	Abdominal Obesity Class 2	*COL4A3BP*	rs4704220	5	74757556	0.48	G/A	0.82 1.12E-08	0.78 3.82E-10	1.27 1.06E-02	1.12E-08	1.06E-02	1.25E-02	EDGxE
Total-C	Abdominal Obesity Class 2	*COL4A3BP*	rs6873472	5	74768347	0.48	C/A	0.82 1.19E-08	0.78 3.93E-10	1.27 1.02E-02	1.19E-08	1.02E-02	1.25E-02	EDGxE
Total-C	Abdominal Obesity Class 2	*HMGCR*	rs6892023	5	74611574	0.48	G/T	0.82 9.55E-09	0.78 3.65E-10	1.26 1.19E-02	9.55E-09	1.19E-02	1.25E-02	EDGxE
Total-C	Abdominal Obesity Class 2	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.81 5.38E-09	0.78 1.97E-10	1.27 1.13E-02	4.04E-08	1.13E-02	1.25E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs11957260	5	74608732	0.48	C/T	0.81 6.61E-09	0.73 4.85E-08	1.20 8.06E-03	6.61E-09	8.06E-03	5.00E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 4.99E-09	0.73 5.08E-08	1.20 8.64E-03	4.99E-09	8.64E-03	5.00E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs3846662	5	74651084	0.48	A/G	0.82 1.47E-08	0.73 8.53E-08	1.20 1.06E-02	1.47E-08	1.06E-02	1.25E-02	CT1/CT2
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs4703667	5	74613906	0.48	G/C	0.81 5.19E-09	0.73 7.91E-08	1.19 1.26E-02	5.19E-09	1.26E-02	5.00E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs4704208	5	74621671	0.48	A/G	0.82 9.57E-09	0.73 8.87E-08	1.20 1.05E-02	9.57E-09	1.05E-02	1.25E-02	CT1/CT2
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs4704210	5	74635225	0.49	G/C	0.82 1.09E-08	0.73 6.45E-08	1.19 1.15E-02	1.09E-08	1.15E-02	1.25E-02	CT1/CT2
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs6892023	5	74611574	0.48	G/T	0.81 7.15E-09	0.73 4.30E-08	1.21 7.42E-03	7.15E-09	7.42E-03	5.00E-02	CT1/CT2
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs7702895	5	74612893	0.48	G/A	0.81 7.29E-09	0.72 3.15E-08	1.22 5.40E-03	7.29E-09	5.44E-03	1.25E-02	CT1/CT2 EDGxE
Total-C	Abdominal Obesity Based on WHR	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.81 4.54E-09	0.73 1.20E-07	1.18 2.14E-02	4.54E-09	2.14E-02	5.00E-02	CT1/CT2 EDGxE
HDL-C	Obesity	*LOC101929680 SCN1A*	rs11885663	2	166944004	0.09	T/C	0.98 6.40E-01	0.93 1.68E-01	2.28 4.38E-08	7.72E-05	3.16E-04	7.63E-07	CO
HDL-C	Obesity	*LOC101929680 SCN1A*	rs11887412	2	166945217	0.08	C/G	0.97 6.03E-01	0.93 1.53E-01	2.30 3.37E-08	2.56E-04	3.13E-04	7.63E-07	CO

Supplemental Table S4. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HDL-C	Obesity	*LOC101929680 SCN1A*	rs11890028	2	166943277	0.09	G/T	0.96 4.19E-01	0.92 8.78E-02	2.30 2.79E-08	1.71E-04	2.51E-04	7.63E-07	CO
HDL-C	Obesity	*LOC101929680 SCN1A*	rs13004083	2	166945367	0.08	G/A	0.98 6.33E-01	0.93 1.66E-01	2.29 3.72E-08	2.71E-04	3.26E-04	7.63E-07	CO
HDL-C	Obesity	*LOC101929680 SCN1A*	rs1972712	2	166945635	0.08	C/T	0.98 6.67E-01	0.93 1.78E-01	2.30 3.15E-08	5.91E-05	2.96E-04	7.63E-07	CO
HDL-C	Obesity	*LOC101929680 SCN1A*	rs1972713	2	166945658	0.08	T/C	0.98 6.62E-01	0.93 1.76E-01	2.30 3.15E-08	6.00E-05	2.93E-04	7.63E-07	CO
LDL-C	Overweight Class 1	*LOC101928271*	rs11693076	2	21140033	0.20	C/T	0.75 1.25E-09	0.96 6.54E-01	0.70 6.79E-04	8.86E-09	6.79E-04	7.81E-04	CT1/CT2 EDGxE
LDL-C	Overweight Class 1	*LOC101928271*	rs6705668	2	21142546	0.20	G/T	0.75 1.81E-09	0.96 6.85E-01	0.70 6.56E-04	1.29E-08	6.56E-04	7.81E-04	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*ANKDD1B*	rs11748027	5	74909972	0.46	C/T	0.77 1.02E-09	0.74 8.14E-11	1.30 2.46E-02	1.02E-09	2.46E-02	5.00E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*HMGCR*	rs11957260	5	74608732	0.48	C/T	0.81 2.08E-09	0.77 5.53E-11	1.30 6.89E-03	2.08E-09	6.89E-03	1.25E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*HMGCR*	rs2878417	5	74617262	0.48	G/A	0.81 2.40E-09	0.78 6.89E-11	1.29 7.46E-03	2.40E-09	7.46E-03	1.25E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*HMGCR*	rs4703667	5	74613906	0.48	G/C	0.81 1.91E-09	0.78 8.68E-11	1.27 1.22E-02	1.91E-09	1.22E-02	1.25E-02	EDGxE
LDL-C	Abdominal Obesity Class 2	*COL4A3BP*	rs4704220	5	74757556	0.48	G/A	0.81 2.09E-09	0.77 5.20E-11	1.30 6.60E-03	2.09E-09	6.60E-03	1.25E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*COL4A3BP*	rs6873472	5	74768347	0.48	C/A	0.81 2.21E-09	0.77 5.40E-11	1.30 6.35E-03	2.21E-09	6.35E-03	1.25E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*HMGCR*	rs6892023	5	74611574	0.48	G/T	0.81 2.23E-09	0.78 6.17E-11	1.29 7.16E-03	2.23E-09	7.16E-03	1.25E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*ANKDD1B*	rs7703282	5	74906963	0.46	A/C	0.77 7.72E-10	0.74 6.12E-11	1.30 2.45E-02	7.72E-10	2.45E-02	5.00E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Class 2	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.80 1.17E-09	0.77 2.61E-11	1.31 5.68E-03	1.17E-09	5.68E-03	5.00E-02	CT1/CT2 EDGxE
LDL-C	Abdominal Obesity Based on WHR	*ANKDD1B*	rs11748027	5	74909972	0.46	C/T	0.77 1.25E-09	0.70 4.99E-08	1.19 4.41E-02	1.25E-09	4.41E-02	5.00E-02	EDGxE
LDL-C	Abdominal Obesity Based on WHR	*HMGCR*	rs2335418	5	74603479	0.43	G/A	0.80 1.36E-09	0.74 6.04E-07	1.16 4.15E-02	1.36E-09	4.39E-02	5.00E-02	CT1/CT2

Supplemental Table S4. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (p-value)	OR_G (p-value)	OR_{GxE} (p-value)	Screen	Test	Cut-Off	
LDL-C	Abdominal Obesity Based on WHR	*ANKDD1B*	rs7703282	5	74906963	0.46	A/C	0.77 9.08E-10	0.70 4.41E-08	1.19 4.57E-02	9.08E-10	4.57E-02	5.00E-02	EDGxE
LDL-C	Abdominal Obesity Based on WHR	*COL4A3BP*	rs7733436	5	74666492	0.48	C/T	0.80 8.91E-10	0.73 3.69E-08	1.18 2.06E-02	8.91E-10	2.06E-02	5.00E-02	CT1/CT2
TG	Overweight Class 1	*BUD13*	rs1558860	11	116607368	0.22	A/C	1.55 5.10E-35	1.76 1.01E-14	0.80 3.27E-03	5.10E-35	7.54E-03	1.25E-02	EDGxE
TG	Overweight Class 1	*BUD13*	rs180349	11	116611827	0.22	A/T	1.53 4.02E-34	1.73 4.27E-14	0.81 5.22E-03	4.02E-34	1.10E-02	1.25E-02	EDGxE
TG	Overweight Class 1	*BUD13*	rs1974718	11	116606766	0.22	G/A	1.54 3.64E-34	1.75 1.94E-14	0.80 3.68E-03	3.64E-34	8.13E-03	1.25E-02	EDGxE
TG	Obesity	*LOC105374079 SLC12A8*	rs7634448	3	124869563	0.06	A/G	0.98 8.09E-01	0.90 1.39E-01	2.71 4.09E-08	7.33E-02	2.63E-06	4.66E-11	CO
TG	Obesity	*LOC105374079 SLC12A8*	rs77008808	3	124868173	0.06	T/C	0.97 6.37E-01	0.89 9.29E-02	2.70 4.33E-08	5.54E-02	3.87E-06	4.66E-11	CO
TG	Abdominal Obesity Class 1	*APOA5*	rs651821	11	116662579	0.29	C/T	1.87 1.56E-73	2.01 5.00E-47	0.81 4.06E-04	1.56E-73	1.26E-02	5.00E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Class 1	*APOA5*	rs662799	11	116663707	0.29	G/A	1.87 8.34E-72	1.99 2.83E-45	0.81 6.86E-04	8.34E-72	1.82E-02	5.00E-02	CT1/CT2
TG	Abdominal Obesity Class 1	*BUD13*	rs918144	11	116633825	0.47	T/C	0.71 4.22E-28	0.66 1.47E-19	1.17 7.75E-03	4.22E-28	1.42E-02	5.00E-02	EDGxE
TG	Abdominal Obesity Based on WHR	*ZPR1(ZNF259)*	rs10750096	11	116656788	0.22	C/A	1.57 2.38E-38	1.81 3.23E-22	0.79 3.22E-04	2.38E-38	1.15E-03	1.25E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs10790162	11	116639104	0.22	A/G	1.55 1.60E-36	1.77 5.99E-21	0.80 8.39E-04	1.60E-36	1.82E-03	1.25E-02	CT1/CT2
TG	Abdominal Obesity Based on WHR	*BUD13*	rs10892020	11	116589652	0.32	G/C	1.36 2.18E-21	1.63 3.47E-17	0.76 1.47E-05	2.18E-21	2.25E-05	7.81E-04	DG1/CT EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs10892023	11	116598248	0.32	T/C	1.37 4.39E-23	1.64 6.36E-18	0.76 1.70E-05	4.39E-23	2.52E-05	3.13E-03	DG1/CT EDGxE
TG	Abdominal Obesity Based on WHR	*ZPR1(ZNF259)*	rs113932726	11	116650638	0.08	T/C	1.96 1.35E-40	2.20 1.45E-20	0.81 2.17E-02	1.35E-40	2.55E-02	5.00E-02	CT1/CT2
TG	Abdominal Obesity Based on WHR	*BUD13*	rs1558860	11	116607368	0.22	A/C	1.55 1.63E-35	1.75 9.36E-20	0.80 7.52E-04	1.63E-35	3.51E-03	1.25E-02	CT1/CT2
TG	Abdominal Obesity Based on WHR	*BUD13*	rs180326	11	116624703	0.22	G/T	1.53 1.67E-34	1.74 1.24E-19	0.81 1.73E-03	1.67E-34	2.79E-03	3.13E-03	CT1/CT2

Supplemental Table S4. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
TG	Abdominal Obesity Based on WHR	*BUD13*	rs180378	11	116588909	0.32	A/G	1.37 8.00E-22	1.65 6.04E-18	0.76 1.26E-05	8.00E-22	1.39E-05	7.81E-04	DG1/CT EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs1974718	11	116606766	0.22	G/A	1.54 1.07E-34	1.75 8.63E-20	0.79 5.29E-04	1.07E-34	2.39E-03	3.13E-03	CT1/CT2
TG	Abdominal Obesity Based on WHR	*BUD13*	rs2008915	11	116603134	0.32	C/G	1.37 4.16E-22	1.63 1.30E-17	0.76 1.60E-05	4.16E-22	2.07E-05	3.13E-03	DG1/CT EDGxE
TG	Abdominal Obesity Based on WHR	*APOA5 ZPR1(ZNF259)*	rs2072560	11	116661826	0.22	T/C	1.53 2.55E-33	1.76 3.04E-20	0.78 2.35E-04	2.55E-33	9.68E-04	3.13E-03	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*APOA5 ZPR1(ZNF259)*	rs2075291	11	116661392	0.08	A/C	1.98 8.80E-42	2.23 4.26E-21	0.82 2.43E-02	8.80E-42	2.69E-02	5.00E-02	CT1/CT2
TG	Abdominal Obesity Based on WHR	*APOA5 ZPR1(ZNF259)*	rs2266788	11	116660686	0.22	G/A	1.55 2.99E-36	1.78 3.51E-21	0.79 4.52E-04	2.99E-36	1.24E-03	1.25E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs3212282	11	116601945	0.32	A/G	1.37 1.03E-22	1.64 9.50E-18	0.76 1.77E-05	1.03E-22	2.57E-05	3.13E-03	DG1/CT EDGxE
TG	Abdominal Obesity Based on WHR	*ZPR1(ZNF259)*	rs3741297	11	116657667	0.08	T/C	1.97 5.43E-41	2.21 1.24E-20	0.81 2.37E-02	5.43E-41	2.80E-02	5.00E-02	CT1/CT2
TG	Abdominal Obesity Based on WHR	*BUD13*	rs3825041	11	116631707	0.22	T/C	1.55 6.91E-36	1.77 9.22E-21	0.80 8.64E-04	6.91E-36	1.61E-03	1.25E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs4938305	11	116588629	0.32	T/C	1.37 5.89E-22	1.64 1.66E-17	0.76 2.64E-05	5.89E-22	2.91E-05	7.81E-04	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*APOA5*	rs651821	11	116662579	0.29	C/T	1.86 6.82E-73	2.26 8.52E-41	0.74 3.92E-06	6.82E-73	1.51E-05	5.00E-02	DG1/CT EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs6589565	11	116640237	0.22	A/G	1.55 1.58E-36	1.77 6.16E-21	0.80 8.31E-04	1.58E-36	1.84E-03	1.25E-02	CT1/CT2
TG	Abdominal Obesity Based on WHR	*ZPR1(ZNF259)*	rs6589566	11	116652423	0.22	G/A	1.56 4.34E-37	1.79 1.65E-21	0.79 4.60E-04	4.34E-37	1.29E-03	1.25E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*APOA5*	rs662799	11	116663707	0.29	G/A	1.86 3.45E-71	2.25 2.82E-39	0.74 7.49E-06	3.45E-71	3.01E-05	5.00E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*ZPR1(ZNF259)*	rs7483863	11	116652491	0.22	A/G	1.56 3.40E-37	1.79 1.08E-21	0.79 3.80E-04	3.40E-37	1.15E-03	1.25E-02	CT1/CT2 EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs7930786	11	116624727	0.22	C/G	1.53 1.17E-34	1.74 8.70E-20	0.81 1.43E-03	1.17E-34	2.52E-03	3.13E-03	CT1/CT2
TG	Abdominal Obesity Based on WHR	*BUD13*	rs9326246	11	116611733	0.22	C/G	1.53 2.46E-34	1.73 1.59E-19	0.81 1.13E-03	2.46E-34	2.76E-03	3.13E-03	CT1/CT2

Supplemental Table S4. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
TG	Abdominal Obesity Based on WHR	*ZPR1(ZNF259)*	rs964184	11	116648917	0.22	G/C	1.55 6.41E-37	1.79 1.74E-21	0.79 4.40E-04	6.41E-37	1.27E-03	1.25E-02	CT1/CT2 EDGxE
Remnant-C	Obesity	*BUD13*	rs2000571	11	116585533	0.30	A/G	1.34 9.27E-18	1.32 2.48E-15	1.38 4.55E-02	9.27E-18	4.55E-02	5.00E-02	EDGxE
Remnant-C	Obesity	*BUD13*	rs7926828	11	116586423	0.31	C/T	1.35 1.76E-18	1.33 5.07E-16	1.37 4.88E-02	1.76E-18	4.88E-02	5.00E-02	EDGxE
Remnant-C	Abdominal Obesity Class 2	*BUD13*	rs180339	11	116617782	0.46	T/C	0.75 8.27E-27	0.74 1.69E-26	1.15 1.61E-02	8.27E-27	1.61E-02	5.00E-02	EDGxE
Remnant-C	Abdominal Obesity Class 2	*BUD13*	rs2075295	11	116628401	0.47	C/T	0.75 1.53E-27	0.73 2.21E-27	1.16 1.16E-02	1.53E-27	1.17E-02	1.25E-02	EDGxE
Remnant-C	Abdominal Obesity Class 2	*BUD13*	rs918144	11	116633825	0.47	T/C	0.75 3.06E-27	0.73 4.35E-27	1.15 1.64E-02	3.06E-27	1.64E-02	5.00E-02	EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*BUD13*	rs10892020	11	116589652	0.32	G/C	1.34 3.05E-25	1.46 7.46E-15	0.84 8.44E-04	3.05E-25	7.49E-03	1.25E-02	EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*BUD13*	rs180378	11	116588909	0.32	A/G	1.35 5.63E-26	1.47 1.92E-15	0.84 1.07E-03	5.63E-26	4.94E-03	1.25E-02	EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*BUD13*	rs2008915	11	116603134	0.32	C/G	1.35 2.33E-26	1.46 2.38E-15	0.84 1.07E-03	2.33E-26	7.06E-03	1.25E-02	EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*BUD13*	rs3212282	11	116601945	0.32	A/G	1.35 1.47E-26	1.47 1.98E-15	0.84 9.70E-04	1.47E-26	7.45E-03	1.25E-02	EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*APOA5*	rs651821	11	116662579	0.29	C/T	1.82 1.52E-87	1.99 4.07E-41	0.82 1.76E-04	1.52E-87	1.14E-02	5.00E-02	CT1/CT2 EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*APOA5*	rs662799	11	116663707	0.29	G/A	1.82 2.85E-86	1.99 2.91E-40	0.82 2.29E-04	2.85E-86	1.35E-02	5.00E-02	CT1/CT2

Supplemental Table S5. Genomic inflation factors observed in GWISs for dyslipidemia

Trait	Environment		Marginal Model	Gene-by-Environment Interaction Model	
			Marginal	Main SNP	Interactive
Total-C	Obesity	Overweight Class 1	1.024001	0.995342	0.985151
		Overweight Class 2	1.024476	1.020683	1.001400
		Obesity	1.028280	1.027328	0.954578
HDL-C	Obesity	Overweight Class 1	1.023527	1.001867	0.992091
		Overweight Class 2	1.026377	1.025426	1.004673
		Obesity	1.030186	1.030663	0.950974
LDL-C	Obesity	Overweight Class 1	1.036399	1.010773	0.982385
		Overweight Class 2	1.033528	1.015011	1.001400
		Obesity	1.033050	1.032572	0.936654
TG	Obesity	Overweight Class 1	1.025902	0.999534	0.992555
		Overweight Class 2	1.029233	1.021630	0.993484
		Obesity	1.031140	1.022578	0.970919
Remnant-C	Obesity	Overweight Class 1	1.021630	0.991628	0.988386
		Overweight Class 2	1.025902	1.013597	1.005610
		Obesity	1.024476	1.018789	0.971833

*** Any inflated results over 1.05 are shown in bold type.**

Supplemental Table S5. Continued

Trait	Environment		Marginal Model	Gene-by-Environment Interaction Model	
			Marginal	Main SNP	Interactive
Total-C	Abdominal Obesity	Abdominal Obesity Class 1	1.025426	1.001867	0.994413
		Abdominal Obesity Class 2	1.028280	1.026853	0.986074
		Abdominal Obesity Based on WHR	1.024476	0.998601	1.006547
HDL-C	Abdominal Obesity	Abdominal Obesity Class 1	1.024001	1.021156	0.995807
		Abdominal Obesity Class 2	1.026377	1.027328	0.991628
		Abdominal Obesity Based on WHR	1.026853	1.004673	0.996738
LDL-C	Abdominal Obesity	Abdominal Obesity Class 1	1.035441	1.026377	0.979165
		Abdominal Obesity Class 2	1.034006	1.032572	0.982845
		Abdominal Obesity Based on WHR	1.033050	1.007485	0.999067
TG	Abdominal Obesity	Abdominal Obesity Class 1	1.025426	1.014540	0.975952
		Abdominal Obesity Class 2	1.031617	1.024476	0.993948
		Abdominal Obesity Based on WHR	1.027328	0.995807	0.979624
Remnant-C	Abdominal Obesity	Abdominal Obesity Class 1	1.020683	1.007954	1.001867
		Abdominal Obesity Class 2	1.023527	1.024951	1.006547
		Abdominal Obesity Based on WHR	1.023052	0.990701	1.011243

*** Any inflated results over 1.05 are shown in bold type.**

Supplemental Table S6. Effects of the interplay between genes and obesity traits on the risk of dyslipidemia

a. Effects of the interplay between *HMGCR* and abdominal obesity based on WHR on the risk of abnormal elevation of Total-C

Abdominal Obesity Based on WHR	Genotype of rs7702895		
	GG (95% CI)	GA (95% CI)	AA (95% CI)
Normal	1.00	0.72 (0.62-0.84)	0.56 (0.45-0.70)
Obese	1.12 (0.96-1.31)	1.05 (0.91-1.21)	0.88 (0.74-1.04)
Multiplicative Effect	1.12 (0.96-1.31)	1.46 (1.28-1.67)	1.57 (1.26-1.95)

b. Effects of the interplay between *LOC101928271* and overweight class 1 on the risk of abnormal elevation of LDL-C

Overweight Class 1	Genotype of rs11693076		
	CC (95% CI)	CT (95% CI)	TT (95% CI)
Normal	1.00	0.98 (0.81-1.19)	0.85 (0.52-1.41)
Obese	1.82 (1.61-2.06)	1.32 (1.14-1.53)	0.85 (0.59-1.24)
Multiplicative Effect	1.82 (1.61-2.06)	1.34 (1.12-1.61)	1.00 (0.54-1.82)

Supplemental Table S6. Continued

c. Effects of the interplay between *BUD13* and abdominal obesity class 1 on the risk of abnormal elevation of TG

Abdominal Obesity Class 1	Genotype of rs918144		
	TT (95% CI)	TC (95% CI)	CC (95% CI)
Normal	1.00	0.75 (0.67-0.84)	0.47 (0.40-0.56)
Obese	1.56 (1.40-1.76)	1.27 (1.14-1.41)	1.00 (0.86-1.15)
Multiplicative Effect	1.56 (1.40-1.76)	1.68 (1.52-1.86)	2.12 (1.76-2.56)

d. Effects of the interplay between *BUD13* and abdominal obesity class 2 on the risk of abnormal elevation of Remnant-C

Abdominal Obesity Class 2	Genotype of rs2075295		
	CC (95% CI)	CT (95% CI)	TT (95% CI)
Normal	1.00	0.81 (0.76-0.87)	0.61 (0.56-0.67)
Obese	1.31 (1.17-1.47)	1.15 (1.04-1.27)	1.08 (0.94-1.25)
Multiplicative Effect	1.31 (1.17-1.47)	1.41 (1.28-1.55)	1.77 (1.51-2.07)

Supplemental Table S6. Continued

e. Effects of the interplay between *LOC101929680/SCN1A* and obesity on the risk of abnormal reduction of HDL-C

Obesity	Genotype of rs11890028		
	GG (95% CI)	GT (95% CI)	TT (95% CI)
Normal	1.00	0.94 (0.86-1.03)	0.77 (0.50-1.20)
Obese	1.42 (1.22-1.65)	1.87 (1.49-2.34)	4.83 (4.66-5.00)
Multiplicative Effect	1.42 (1.22-1.65)	1.99 (1.57-2.52)	6.24 (4.03-9.64)

f. Effects of the interplay between *APOA5* and abdominal obesity based on WHR on the risk of abnormal elevation of TG

Abdominal Obesity Based on WHR	Genotype of rs651821		
	CC (95% CI)	CT (95% CI)	TT (95% CI)
Normal	1.00	2.08 (1.76-2.46)	4.13 (3.37-5.05)
Obese	2.56 (2.20-2.99)	3.93 (3.39-4.57)	5.73 (4.83-6.80)
Multiplicative Effect	2.56 (2.20-2.99)	1.89 (1.68-2.12)	1.39 (1.16-1.66)

Supplemental Table S6. Continued

g. Effects of the interplay between *APOA5* and abdominal obesity based on WHR on the risk of abnormal elevation of Remnant-C

Abdominal Obesity Based on WHR	Genotype of rs651821		
	CC (95% CI)	CT (95% CI)	TT (95% CI)
Normal	1.00	1.74 (1.53-1.97)	3.05 (2.61-3.57)
Obese	2.20 (1.96-2.46)	3.21 (2.88-3.59)	4.51 (3.98-5.11)
Multiplicative Effect	2.20 (1.96-2.46)	1.85 (1.69-2.03)	1.48 (1.28-1.71)

Supplemental Table S7. Changes in HDL-C and TG due to an increment of BMI of 1 kg/m^2 for each risk group

Trait	Risk Group	Total			Normal (18.5≤BMI<25.0 kg/m^2)			Overweight Class 1 (23.0 kg/m^2≤BMI)			Overweight Class 2 (25.0 kg/m^2≤BMI)		
		Individuals (%)	Effect (mmol/L)	*p*-value	Individuals (%)	Effect (mmol/L)	*p*-value	Individuals (%)	Effect (mmol/L)	*p*-value	Individuals (%)	Effect (mmol/L)	*p*-value
HDL-C	Low	13,091 (83.1)	-0.023±0.001	-	8,182 (83.1)	-0.032±0.002	-	8,390 (83.1)	-0.013±0.001	-	4,909 (83.1)	-0.004±0.002	-
	High	2,663 (16.9)	-0.026±0.002	5.61E-02	1,668 (16.9)	-0.039±0.004	7.93E-02	1,709 (16.9)	-0.016±0.003	1.11E-01	995 (16.9)	-0.014±0.004	7.58E-04
	Higher	1,331 (8.4)	-0.027±0.002	1.07E-01	836 (8.5)	-0.038±0.005	7.93E-02	862 (8.5)	-0.019±0.004	1.11E-01	495 (8.4)	-0.017±0.005	7.58E-04
TG	Low	14,007 (88.9)	0.072±0.003	-	8,762 (89.0)	0.087±0.005	-	8,939 (88.5)	0.055±0.005	-	5,245 (88.8)	0.034±0.008	-
	High	1,747 (11.1)	0.070±0.007	9.60E-01	1,088 (11.0)	0.054±0.014	6.11E-02	1,160 (11.5)	0.088±0.012	3.06E-03	659 (11.2)	0.080±0.018	7.81E-03
	Higher	875 (5.6)	0.078±0.010	5.92E-01	548 (5.6)	0.081±0.022	6.11E-02	574 (5.7)	0.095±0.019	3.06E-03	327 (5.5)	0.089±0.022	7.81E-03

Individuals were classified into three risk groups based on the number of risk alleles at GxE loci. Individuals with no risk alleles were classified into the low-risk group; individuals with at least one risk allele were classified into the high-risk group; the upper 50% of people belong to the high-risk group were classified into the higher-risk group.

Supplemental Table S8. Gene-by-lifestyle interactive loci of hypertension obtained from the meta-analysis of the cohorts

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HBP-S1	Ever Smoking	*DCC*	rs9950661	18	50627680	0.34	C/T	0.87 9.85E-08	0.89 1.25E-04	0.90 3.54E-02	9.85E-08	4.95E-02	5.00E-02	CT1
HBP-S1	Ever Smoking	*DCC*	rs9950661	18	50627680	0.34	C/T	0.87 9.85E-08	0.89 1.25E-04	0.90 3.54E-02	9.85E-08	4.95E-02	5.00E-02	CT2
HBP-S1	Ever Drinking	*SORCS3*	rs790647	10	106776484	0.22	A/C	0.98 4.71E-01	1.19 8.00E-05	0.71 3.34E-09	9.60E-01	3.34E-09	1.82E-13	CC
HBP-S1	Ever Drinking	*RP1-71H24.1*	rs10774681	12	113450032	0.47	G/A	1.02 3.27E-01	0.96 2.25E-01	1.35 3.39E-16	3.20E-17	1.66E-02	7.63E-07	CO
HBP-S1	Ever Drinking	*RP1-71H24.1*	rs10774681	12	113450032	0.47	G/A	1.02 3.27E-01	0.96 2.25E-01	1.35 3.39E-16	3.20E-17	1.66E-02	5.00E-02	EDGxE
HBP-S1	Ever Drinking	*RP1-71H24.1*	rs10850108	12	113414040	0.32	C/T	1.01 8.10E-01	0.94 9.77E-02	1.33 1.55E-12	2.07E-11	1.89E-02	7.63E-07	CO
HBP-S1	Ever Drinking	*USP30*	rs117658137	12	109473666	0.02	G/T	0.99 9.27E-01	1.06 6.31E-01	0.47 3.47E-08	4.47E-10	5.55E-01	7.63E-07	CO
HBP-S1	Ever Drinking	*RPH3A*	rs12581345	12	113257970	0.25	C/T	1.05 1.09E-01	0.98 6.09E-01	1.30 5.92E-10	5.67E-12	4.95E-02	7.63E-07	CO
HBP-S1	Ever Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.86 9.64E-05	0.94 2.42E-01	0.29 1.17E-84	1.25E-140	9.18E-03	5.00E-02	CT2
HBP-S1	Ever Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.86 9.64E-05	0.94 2.42E-01	0.29 1.17E-84	1.25E-140	9.18E-03	5.00E-02	EDGxE
HBP-S1	Ever Drinking	*RPH3A*	rs3782880	12	113235589	0.16	T/C	1.01 7.83E-01	0.94 2.80E-01	1.39 5.96E-09	5.26E-10	1.17E-01	7.63E-07	CO
HBP-S1	Ever Drinking	*GIT2*	rs4766646	12	110398145	0.34	A/T	0.98 4.94E-01	0.94 9.18E-02	1.28 6.22E-10	2.06E-12	1.20E-01	7.63E-07	CO
HBP-S1	Ever Drinking	*RP3-473L9.4*	rs56663449	12	111809182	0.13	A/G	0.99 8.60E-01	0.88 7.55E-02	1.54 1.18E-09	9.68E-11	3.55E-02	7.63E-07	CO
HBP-S1	Ever Drinking	*MVK*	rs61940559	12	110051124	0.06	T/C	0.99 8.47E-01	1.11 1.36E-01	0.55 6.32E-15	2.29E-16	2.05E-02	7.63E-07	CO
HBP-S1	Ever Drinking	*RP3-473L9.4*	rs7298118	12	111837285	0.16	A/G	1.00 9.04E-01	0.91 1.30E-01	1.63 1.54E-16	3.32E-18	6.92E-02	7.63E-07	CO
HBP-S1	Ever Drinking	*HECTD4*	rs77215829	12	112618346	0.23	C/A	1.02 4.07E-01	0.94 1.73E-01	1.44 2.31E-16	5.65E-22	1.63E-02	5.00E-02	EDGxE
HBP-S1	Ever Drinking	*MYL2*	rs7957741	12	111363516	0.46	C/T	1.02 5.12E-01	0.94 1.50E-01	1.53 1.05E-19	1.38E-27	1.70E-02	5.00E-02	EDGxE

Supplemental Table S8. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HBP-S1	Ever Drinking	*TRPV4*	rs7971845	12	110260702	0.22	G/C	1.00 8.98E-01	0.93 1.61E-01	1.37 1.15E-10	4.15E-12	8.81E-02	7.63E-07	CO
HBP-S1	Current Drinking	*RP1-71H24.1*	rs10774681	12	113450032	0.47	G/A	1.02 3.78E-01	0.98 5.49E-01	1.29 8.47E-13	4.64E-15	9.12E-02	7.63E-07	CO
HBP-S1	Current Drinking	*RP1-71H24.1*	rs10850108	12	113414040	0.32	C/T	1.00 8.57E-01	0.94 1.12E-01	1.28 2.10E-10	4.63E-09	1.65E-02	7.63E-07	CO
HBP-S1	Current Drinking	*HVCN1*	rs11065687	12	111075823	0.42	C/T	0.99 5.74E-01	0.93 2.63E-02	1.22 4.81E-08	3.36E-07	1.45E-02	7.63E-07	CO
HBP-S1	Current Drinking	*LHX5*	rs11066630	12	114041467	0.03	A/G	0.91 1.48E-01	1.02 7.94E-01	0.49 1.76E-11	6.85E-13	3.56E-02	7.63E-07	CO
HBP-S1	Current Drinking	*RPH3A*	rs12297016	12	113260801	0.25	A/G	1.04 1.40E-01	0.97 5.22E-01	1.26 1.81E-08	6.15E-10	2.20E-02	7.63E-07	CO
HBP-S1	Current Drinking	*MVK*	rs1420749	12	110081884	0.15	C/T	0.99 8.51E-01	1.02 7.34E-01	0.76 2.17E-08	7.46E-10	4.55E-01	7.63E-07	CO
HBP-S1	Current Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.87 3.14E-04	0.94 1.70E-01	0.32 6.45E-75	6.18E-125	1.16E-02	5.00E-02	CT2
HBP-S1	Current Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.87 3.14E-04	0.94 1.70E-01	0.32 6.45E-75	6.18E-125	1.16E-02	5.00E-02	EDGxE
HBP-S1	Current Drinking	*RPH3A*	rs3782880	12	113235589	0.16	T/C	1.01 8.60E-01	0.93 2.34E-01	1.35 3.14E-08	2.33E-09	7.71E-02	7.63E-07	CO
HBP-S1	Current Drinking	*MYO1H*	rs58832357	12	109856190	0.07	G/A	0.97 4.97E-01	1.03 5.91E-01	0.67 1.24E-08	8.17E-11	1.26E-01	7.63E-07	CO
HBP-S1	Current Drinking	*BRAP*	rs601663	12	112123284	0.05	A/G	1.12 2.82E-02	1.08 3.33E-01	1.52 4.90E-08	9.01E-10	4.58E-01	7.63E-07	CO
HBP-S1	Current Drinking	*MVK*	rs61940559	12	110051124	0.06	T/C	1.00 9.21E-01	1.11 1.04E-01	0.55 2.21E-15	3.15E-16	8.06E-03	7.63E-07	CO
HBP-S1	Current Drinking	*ATXN2*	rs678436	12	111949394	0.06	T/C	1.11 4.47E-02	1.02 7.72E-01	1.51 3.43E-08	1.99E-09	1.34E-01	7.63E-07	CO
HBP-S1	Current Drinking	*RP3-473L9.4*	rs7298118	12	111837285	0.16	A/G	0.99 8.24E-01	0.89 3.93E-02	1.58 3.09E-16	1.87E-15	9.56E-03	7.63E-07	CO
HBP-S1	Current Drinking	*FAM109A*	rs73412354	12	111804471	0.13	T/C	0.99 8.13E-01	0.93 2.17E-01	1.41 3.39E-08	1.47E-10	1.43E-01	7.63E-07	CO
HBP-S1	Current Drinking	*TRPV4*	rs7971845	12	110260702	0.22	G/C	0.99 8.34E-01	0.91 6.06E-02	1.33 8.48E-10	4.69E-09	1.66E-02	7.63E-07	CO

Supplemental Table S8. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HBP-S1	Current Drinking	*CUX2*	rs933306	12	111737985	0.08	A/T	1.01 8.40E-01	0.93 2.46E-01	1.44 1.20E-08	3.15E-09	6.70E-02	7.63E-07	CO
HBP-S1	Moderate Drinking	*KLF4*	rs79977578	9	110833870	0.09	G/T	0.97 4.74E-01	1.19 1.63E-03	0.60 7.81E-09	1.48E-01	7.81E-09	1.16E-11	CC
HBP-S1	Moderate Drinking	*KLF4*	rs79977578	9	110833870	0.09	G/T	0.97 4.74E-01	1.19 1.63E-03	0.60 7.81E-09	1.48E-01	7.81E-09	1.16E-11	EB
HBP-S1	Moderate Drinking	*RP3-473L9.4*	rs11065889	12	111829557	0.19	T/A	1.02 5.47E-01	0.98 6.66E-01	1.29 1.95E-09	3.48E-11	1.57E-01	1.22E-05	CO
HBP-S1	Moderate Drinking	*MVK*	rs11067592	12	110069190	0.04	T/G	0.97 6.68E-01	1.02 7.96E-01	0.52 4.05E-08	9.73E-11	1.19E-01	4.88E-05	CO
HBP-S1	Moderate Drinking	*CUX2*	rs1265566	12	111716376	0.33	C/T	1.03 2.08E-01	0.98 6.30E-01	1.25 1.70E-10	8.60E-11	2.09E-02	1.22E-05	CO
HBP-S1	Moderate Drinking	*CUX2*	rs1265566	12	111716376	0.33	C/T	1.03 2.73E-01	1.01 7.35E-01	1.26 3.41E-09	1.87E-12	2.22E-01	4.88E-05	CO
HBP-S1	Moderate Drinking	*RP3-473L9.4*	rs4766460	12	111835009	0.17	A/G	1.02 5.28E-01	1.00 9.22E-01	1.34 3.48E-09	2.89E-11	3.79E-01	4.88E-05	CO
HBP-S1	Moderate Drinking	*RPH3A*	rs4767019	12	113289070	0.38	G/A	0.93 2.44E-03	0.90 2.41E-04	0.81 2.52E-07	2.92E-20	2.65E-02	5.00E-02	EDGxE
HBP-S1	Low-Risk Drinking	*BRAP*	rs10774633	12	112096289	0.4	C/T	1.05 3.87E-02	1.04 1.44E-01	1.43 3.71E-10	7.47E-13	5.89E-02	1.95E-04	CO
HBP-S1	Low-Risk Drinking	*CUX2*	rs10849933	12	111757647	0.32	A/C	1.03 3.39E-01	1.01 7.38E-01	1.45 2.47E-08	2.47E-08	3.70E-02	1.22E-05	CO
HBP-S1	Low-Risk Drinking	*SH2B3*	rs11065905	12	111887974	0.46	G/A	1.05 1.08E-01	1.03 2.55E-01	1.46 3.84E-08	5.92E-11	1.39E-01	1.22E-05	CO
HBP-S1	Low-Risk Drinking	*MAPKAPK5*	rs11066065	12	112329287	0.44	C/G	1.06 1.29E-02	1.05 5.53E-02	1.44 1.21E-10	1.97E-14	8.65E-02	3.13E-03	CO
HBP-S1	Low-Risk Drinking	*HECTD4*	rs11066230	12	112715324	0.39	G/A	1.06 2.83E-02	1.04 9.79E-02	1.39 5.29E-09	6.03E-12	1.09E-01	4.88E-05	CO
HBP-S1	Low-Risk Drinking	*PTPN11*	rs11066315	12	112895141	0.4	G/A	1.07 6.06E-03	1.06 2.58E-02	1.38 2.19E-08	2.74E-11	1.56E-01	1.22E-05	CO
HBP-S1	Low-Risk Drinking	*C12orf51*	rs12579396	12	112594814	0.39	C/T	1.06 1.58E-02	1.05 6.10E-02	1.39 4.56E-09	5.97E-12	1.16E-01	4.88E-05	CO
HBP-S1	Low-Risk Drinking	*CUX2*	rs4766542	12	111590492	0.49	T/C	1.06 1.75E-02	1.05 3.77E-02	1.36 3.64E-08	1.89E-11	4.41E-01	4.88E-05	CO

Supplemental Table S8. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HBP-S1	Low-Risk Drinking	*RPH3A*	rs886476	12	113319471	0.37	G/A	0.91 3.52E-04	0.93 9.03E-03	0.64 1.33E-12	3.52E-04	1.79E-03	1.91E-07	CO
HBP-S1	Low-Risk Drinking	*RPH3A*	rs886476	12	113319471	0.37	G/A	0.91 3.52E-04	0.93 9.03E-03	0.64 1.33E-12	7.91E-15	1.58E-03	3.13E-03	CT2
HBP-S1	Low-Risk Drinking	*RPH3A*	rs886476	12	113319471	0.37	G/A	0.91 3.52E-04	0.93 9.03E-03	0.64 1.33E-12	1.11E-16	1.58E-03	3.13E-03	EDGxE
HBP-S1	Heavy Drinking	*TMEM116*	rs1016079	12	112410186	0.23	G/T	1.03 3.42E-01	1.01 6.54E-01	1.41 2.85E-10	3.94E-12	2.06E-01	1.22E-05	CO
HBP-S1	Heavy Drinking	*BRAP*	rs10774633	12	112096289	0.4	C/T	1.05 6.06E-02	1.03 2.79E-01	1.42 5.23E-13	4.87E-17	4.21E-02	4.88E-05	CO
HBP-S1	Heavy Drinking	*BRAP*	rs10774633	12	112096289	0.4	C/T	1.05 6.06E-02	1.03 2.79E-01	1.42 5.23E-13	4.87E-17	4.21E-02	5.00E-02	EDGxE
HBP-S1	Heavy Drinking	*MAPKAPK5*	rs11066044	12	112283546	0.22	T/C	1.04 2.25E-01	1.02 4.86E-01	1.41 2.15E-10	4.10E-12	2.07E-01	1.22E-05	CO
HBP-S1	Heavy Drinking	*MAPKAPK5*	rs11066058	12	112317320	0.22	C/T	1.02 3.93E-01	1.01 7.33E-01	1.41 4.10E-10	8.32E-12	1.91E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*HECTD4*	rs11066272	12	112802224	0.23	T/A	1.04 2.37E-01	1.02 5.58E-01	1.47 1.64E-09	2.61E-10	1.30E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*PTPN11*	rs11066315	12	112895141	0.4	G/A	1.07 1.05E-02	1.05 6.86E-02	1.41 2.82E-12	2.01E-16	8.90E-02	1.22E-05	CO
HBP-S1	Heavy Drinking	*UBE3B*	rs11066855	12	109922307	0.03	T/C	0.96 5.78E-01	0.98 7.66E-01	0.36 3.27E-08	3.50E-10	3.01E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*ALDH2*	rs112605264	12	112249140	0.4	A/C	1.05 6.68E-02	1.03 3.00E-01	1.41 5.48E-13	5.62E-17	4.25E-02	4.88E-05	CO
HBP-S1	Heavy Drinking	*ALDH2*	rs11613713	12	112217138	0.22	T/C	1.02 4.18E-01	1.01 8.41E-01	1.42 1.10E-10	6.22E-12	1.11E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*NAA25*	rs12312538	12	112489521	0.22	C/T	1.03 3.19E-01	1.01 6.43E-01	1.41 2.08E-10	4.75E-12	1.79E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*TMEM116*	rs16941759	12	112367921	0.22	A/G	1.03 3.67E-01	1.01 7.00E-01	1.41 3.65E-10	6.66E-12	1.87E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*MYL2*	rs4766517	12	111359712	0.49	C/G	1.00 9.00E-01	0.97 3.19E-01	1.38 4.63E-10	3.50E-10	7.48E-03	3.05E-06	CO
HBP-S1	Heavy Drinking	*MYL2*	rs4766527	12	111405470	0.43	G/T	0.99 7.13E-01	0.98 3.32E-01	1.33 1.73E-09	1.14E-11	6.79E-02	3.05E-06	CO

Supplemental Table S8. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HBP-S1	Heavy Drinking	*CUX2*	rs55794686	12	111701329	0.48	G/T	1.04 1.18E-01	1.03 2.89E-01	1.43 6.10E-11	1.60E-14	2.29E-01	1.22E-05	CO
HBP-S1	Heavy Drinking	*TRAFD1*	rs7970397	12	112580071	0.22	T/C	1.02 4.60E-01	1.01 8.46E-01	1.41 2.23E-10	5.83E-12	1.54E-01	3.05E-06	CO
HBP-S1	Heavy Drinking	*RPH3A*	rs886476	12	113319471	0.37	G/A	0.92 6.01E-04	0.94 1.51E-02	0.71 1.66E-11	6.01E-04	1.11E-02	4.77E-08	CO
HBP-S1	Heavy Drinking	*CUX2*	rs916683	12	111616207	0.42	C/G	1.06 2.56E-02	1.04 1.39E-01	1.35 6.03E-10	5.66E-12	6.37E-02	3.05E-06	CO
HBP-S1	Binge Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.87 1.21E-04	0.87 2.33E-04	0.37 1.51E-09	1.21E-04	2.72E-01	7.63E-07	CO
HBP-S1	Binge Drinking	*CCDC63*	rs7311323	12	111323939	0.16	G/A	0.95 1.25E-01	0.96 1.86E-01	0.48 2.49E-09	8.53E-13	2.09E-01	3.13E-03	CO
HBP-S1	Obesity	*SNORA40*	rs16923092	10	23447523	0.06	A/C	0.99 9.03E-01	0.98 7.23E-01	1.98 5.26E-09	2.66E-08	2.47E-01	5.00E-02	CO
HBP-S2	Ever Drinking	*MYL2*	rs12229654	12	111414461	0.14	G/T	0.90 1.55E-02	0.98 7.23E-01	0.20 4.24E-58	2.24E-194	2.12E-02	5.00E-02	CT1
HBP-S2	Ever Drinking	*MYL2*	rs12229654	12	111414461	0.14	G/T	0.90 1.55E-02	0.98 7.23E-01	0.20 4.24E-58	2.24E-194	2.12E-02	5.00E-02	CT2
HBP-S2	Ever Drinking	*MYO1H*	rs144087593	12	109854841	0.05	C/T	1.01 8.83E-01	1.20 4.10E-02	0.45 2.10E-09	6.07E-18	6.47E-03	5.00E-02	EDGxE
HBP-S2	Current Drinking	*MYO1H*	rs11066562	12	109869385	0.04	A/G	1.08 2.35E-01	1.28 3.43E-03	0.42 1.75E-10	2.86E-20	2.21E-03	5.00E-02	EDGxE
HBP-S2	Current Drinking	*MVK*	rs11067475	12	110046648	0.04	A/G	1.05 4.49E-01	1.26 8.94E-03	0.39 3.77E-11	8.39E-21	1.76E-03	5.00E-02	EDGxE
HBP-S2	Current Drinking	*MYL2*	rs12229654	12	111414461	0.14	G/T	0.90 2.49E-02	0.99 7.98E-01	0.24 6.54E-51	1.52E-161	8.95E-03	5.00E-02	CT1
HBP-S2	Current Drinking	*MYL2*	rs12229654	12	111414461	0.14	G/T	0.90 2.49E-02	0.99 7.98E-01	0.24 6.54E-51	1.52E-161	8.95E-03	5.00E-02	CT2
HBP-S2	Current Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.89 1.28E-02	0.96 4.67E-01	0.31 9.38E-33	6.18E-125	2.85E-02	5.00E-02	CT1
HBP-S2	Current Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	0.89 1.28E-02	0.96 4.67E-01	0.31 9.38E-33	6.18E-125	2.85E-02	5.00E-02	CT2
HBP-S2	Obesity	*ST5*	rs140343181	11	8763373	0.01	A/G	0.90 3.96E-01	0.79 9.39E-02	4.23 3.75E-08	3.50E-06	5.27E-03	7.81E-04	CO

Supplemental Table S8. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	Exhaustive Scan		Two-Step Method			Test
								OR_D (*p*-value)	OR_G (*p*-value)	OR_{GxE} (*p*-value)	Screen	Test	Cut-Off	
HBP-S2	Obesity	*RP11-981P6.1*	rs1689040	12	89978233	0.39	T/C	0.86 2.19E-07	0.85 2.79E-08	1.34 2.29E-02	1.39E-06	2.29E-02	5.00E-02	EDGxE
HBP-S2	Abdominal Obesity Class 1	*ATP2B1*	rs2681472	12	90008959	0.38	G/A	0.85 7.98E-08	0.82 1.32E-06	1.13 2.17E-02	7.98E-08	2.33E-02	5.00E-02	CT1
HBP-S2	Abdominal Obesity Class 1	*ATP2B1*	rs2681472	12	90008959	0.38	G/A	0.85 7.98E-08	0.82 1.32E-06	1.13 2.17E-02	7.98E-08	2.33E-02	5.00E-02	CT2
HBP-S2	Abdominal Obesity Based on WHR	*MYL2*	rs12229654	12	111414461	0.14	G/T	0.89 8.20E-03	0.80 1.58E-03	1.20 4.53E-02	1.01E-06	4.53E-02	5.00E-02	EDGxE

Supplemental Table S9. Genomic inflation factors observed in GWISs for hypertension

Trait	Environment		Marginal Model	Gene-by-Environment Interaction Model	
			Marginal	Main SNP	Interactive
HBP-S1	Cigarette Smoking	Ever Smoking	1.048906	1.010773	1.006547
		Current Smoking	1.048906	1.024951	1.014068
	Alcohol Consumption	Ever Drinking	1.048423	1.017844	0.999534
		Current Drinking	1.048906	1.021156	0.998135
		Moderate Drinking	1.048423	1.038795	1.003270
		Low-Risk Drinking	**1.050356***	1.047457	0.990701
		Heavy Drinking	**1.050356***	1.044564	0.982845
		Binge Drinking	**1.050356***	1.045046	0.935319
	Obesity	Underweight	**1.053261***	**1.053746***	0.926015
		Overweight Class 1	1.048906	1.000233	0.971833
		Overweight Class 2	1.049389	1.026377	0.989311
		Obesity	**1.057143***	**1.060062***	0.962724
	Abdominal Obesity	Abdominal Obesity Class 1	**1.050840***	1.038316	0.990237
		Abdominal Obesity Class 2	**1.051324***	**1.055201***	1.009363
		Abdominal Obesity Based on WHR	**1.050356***	1.019736	1.021156

*** Any inflated results over 1.05 are shown in bold type.**

Supplemental Table S9. Continued

Trait	Environment		Marginal Model	Gene-by-Environment Interaction Model	
			Marginal	Main SNP	Interactive
HBP-S2	Cigarette Smoking	Ever Smoking	1.037836	1.017844	1.011714
		Current Smoking	1.037836	1.015955	0.997669
	Alcohol Consumption	Ever Drinking	1.036399	1.018317	1.004205
		Current Drinking	1.036878	1.013126	1.001400
		Moderate Drinking	1.036399	1.026853	0.992091
		Low-Risk Drinking	1.037836	1.033050	1.022578
		Heavy Drinking	1.038316	1.028757	1.034963
		Binge Drinking	1.038795	1.030186	0.985613
	Obesity	Underweight	1.035920	1.041676	0.933542
		Overweight Class 1	1.036878	0.987923	0.991164
		Overweight Class 2	1.045527	1.010773	1.012655
		Obesity	1.041196	1.041676	1.014068
	Abdominal Obesity	Abdominal Obesity Class 1	1.037836	1.021630	1.007016
		Abdominal Obesity Class 2	1.039275	1.030186	0.991164
		Abdominal Obesity Based on WHR	1.041676	0.994878	0.969550

*** Any inflated results over 1.05 are shown in bold type.**

Supplemental Table S10. Effects of the interplay between genes and lifestyle factors on the risk of hypertension

a. Effects of the interplay between *DCC* and ever smoking on the risk of HBP-S1

Cigarette Smoking	Genotype of rs9950661		
	TT (95% CI)	TC (95% CI)	CC (95% CI)
Normal	1.00	0.97 (0.94-1.01)	0.89 (0.83-0.95)
Ever Smoking	1.22 (1.17-1.27)	1.13 (1.08-1.18)	1.09 (1.01-1.17)
Multiplicative Effect	1.22 (1.17-1.27)	1.16 (1.11-1.21)	1.23 (1.12-1.35)

b. Effects of the interplay between *RPH3A* and low-risk drinking on the risk of HBP-S1

Alcohol Consumption	Genotype of rs886476		
	AA (95% CI)	AG (95% CI)	GG (95% CI)
Normal	1.00	0.98 (0.95-1.01)	0.94 (0.90-0.99)
Low-Risk Drinking	1.27 (1.19-1.34)	1.11 (1.03-1.20)	1.04 (0.88-1.22)
Multiplicative Effect	1.27 (1.19-1.34)	1.13 (1.05-1.22)	1.11 (0.94-1.30)

Supplemental Table S10. Continued

c. Effects of the interplay between *MYL2* and heavy drinking on the risk of HBP-S1

Alcohol Consumption	Genotype of rs4766517		
	GG (95% CI)	GC (95% CI)	CC (95% CI)
Normal	1.00	0.99 (0.95-1.03)	0.97 (0.92-1.01)
Heavy Drinking	1.14 (1.05-1.24)	1.20 (1.13-1.27)	1.28 (1.20-1.36)
Multiplicative Effect	1.14 (1.05-1.24)	1.21 (1.14-1.27)	1.33 (1.24-1.42)

d. Effects of the interplay between *KLF4* and moderate drinking on the risk of HBP-S1

Alcohol Consumption	Genotype of rs79977578		
	TT (95% CI)	TG (95% CI)	GG (95% CI)
Normal	1.00	1.08 (1.03-1.13)	1.14 (0.93-1.40)
Moderate Drinking	1.06 (1.02-1.09)	0.87 (0.81-0.93)	1.09 (0.86-1.38)
Multiplicative Effect	1.06 (1.02-1.09)	0.81 (0.74-0.87)	0.95 (0.70-1.30)

Supplemental Table S10. Continued

e. Effects of the interplay between *RP11-981P6.1* and obesity on the risk of HBP-S2

Obesity	Genotype of rs1689040		
	CC (95% CI)	CT (95% CI)	TT (95% CI)
Normal	1.00	0.84 (0.79-0.90)	0.80 (0.72-0.88)
Obese	1.69 (1.44-1.99)	1.84 (1.60-2.11)	1.89 (1.51-2.36)
Multiplicative Effect	1.69 (1.44-1.99)	2.18 (1.90-2.51)	2.37 (1.87-3.00)

f. Effects of the interplay between *ATP2B1* and abdominal obesity class 1 on the risk of HBP-S2

Abdominal Obesity Class 1	Genotype of rs2681472		
	AA (95% CI)	AG (95% CI)	GG (95% CI)
Normal	1.00	0.81 (0.74-0.89)	0.76 (0.66-0.87)
Obese	1.47 (1.35-1.61)	1.32 (1.21-1.44)	1.31 (1.16-1.48)
Multiplicative Effect	1.47 (1.35-1.61)	1.63 (1.50-1.78)	1.73 (1.47-2.03)

Supplemental Table S10. Continued

g. Effects of the interplay between *MYL2* and abdominal obesity based on WHR on the risk of HBP-S2

Abdominal Obesity Based on WHR	Genotype of rs12229654		
	TT (95% CI)	TG (95% CI)	GG (95% CI)
Normal	1.00	0.87 (0.77-0.98)	0.74 (0.47-1.14)
Obese	1.78 (1.66-1.91)	1.69 (1.55-1.85)	1.97 (1.59-2.45)
Multiplicative Effect	1.78 (1.66-1.91)	1.95 (1.72-2.21)	2.68 (1.65-4.35)

Supplemental Table S11. Gene-by-obesity interactions on quantitative lipid levels

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)	
Total-C	Abdominal Obesity Based on WHR	*HMGCR*	rs7702895	5	74612893	0.48	G/A	-0.08 2.24E-17	-0.11 3.41E-14	0.05 8.90E-03	EDGxE
HDL-C	Overweight Class 1	*LPL*	rs7826306	8	19900671	0.33	C/G	0.03 4.04E-21	0.04 8.12E-15	-0.02 4.81E-03	EDGxE
HDL-C	Overweight Class 1	*ABCA1*	rs1883025	9	107664301	0.24	T/C	-0.04 1.72E-19	-0.05 4.22E-14	0.02 4.92E-03	EDGxE
HDL-C	Overweight Class 2	*LPL*	rs2197089	8	19826373	0.32	A/G	0.03 5.47E-18	0.04 8.31E-17	-0.02 9.73E-03	EDGxE
HDL-C	Abdominal Obesity Based on WHR	*LPL*	rs894210	8	19865843	0.33	A/G	0.03 6.60E-21	0.04 1.07E-18	-0.02 3.79E-04	EDGxE
HDL-C	Abdominal Obesity Based on WHR	*ABCA1*	rs1883025	9	107664301	0.24	T/C	-0.03 1.99E-17	-0.05 1.83E-16	0.03 2.58E-04	EDGxE
LDL-C	Abdominal Obesity Based on WHR	*HMGCR*	rs7702895	5	74612893	0.48	G/A	-0.07 3.23E-16	-0.10 9.78E-15	0.06 1.86E-03	EDGxE
TG	Overweight Class 1	*BUD13*	rs2000571	11	116585533	0.30	A/G	0.07 9.70E-25	0.04 9.85E-05	0.04 1.09E-02	EDGxE
TG	Overweight Class 1	*BUD13*	rs2041967	11	116645149	0.42	G/A	-0.06 6.59E-31	-0.04 5.86E-06	-0.03 3.13E-03	EDGxE
TG	Overweight Class 1	*APOA5*	rs2075291	11	116661392	0.08	A/C	0.18 3.52E-76	0.15 4.32E-19	0.05 1.00E-02	EDGxE
TG	Overweight Class 1	*APOA5*	rs651821	11	116662579	0.29	C/T	0.15 2.42E-140	0.12 9.15E-37	0.04 2.12E-03	EDGxE
TG	Obesity	*APOA5*	rs651821	11	116662579	0.29	C/T	0.15 5.64E-132	0.15 5.31E-123	0.07 2.43E-02	EDGxE
TG	Abdominal Obesity Based on WHR	*BUD13*	rs1240776	11	116536281	0.31	T/C	-0.05 4.83E-21	-0.07 1.64E-14	0.02 4.87E-02	EDGxE
TG	Abdominal Obesity Based on WHR	*SIK3*	rs7115583	11	116784376	0.15	T/G	-0.06 3.19E-17	-0.08 7.23E-13	0.03 3.73E-02	EDGxE

Supplemental Table S11. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)	
Remnant-C	Overweight Class 1	*BUD13*	rs17119975	11	116634557	0.20	C/T	-0.07 3.38E-28	-0.04 3.23E-05	-0.04 2.64E-03	EDGxE
Remnant-C	Overweight Class 1	*BUD13*	rs2041967	11	116645149	0.42	G/A	-0.06 6.57E-34	-0.04 9.68E-06	-0.04 3.57E-04	EDGxE
Remnant-C	Overweight Class 1	*APOA5*	rs2075291	11	116661392	0.08	A/C	0.17 4.50E-73	0.10 1.60E-10	0.11 5.77E-08	DG2/H2/EDGxE
Remnant-C	Overweight Class 1	*APOA5*	rs651821	11	116662579	0.29	C/T	0.13 2.12E-125	0.10 1.16E-26	0.05 5.98E-06	DG2/H2/EDGxE
Remnant-C	Overweight Class 2	*APOA5*	rs2075291	11	116661392	0.08	A/C	0.17 4.79E-72	0.14 1.47E-31	0.08 1.07E-04	EDGxE
Remnant-C	Overweight Class 2	*APOA5*	rs651821	11	116662579	0.29	C/T	0.13 1.28E-124	0.11 1.07E-61	0.04 2.69E-04	EDGxE
Remnant-C	Abdominal Obesity Class 2	*IGSF11*	rs138967034	3	118600140	0.01	T/A	0.05 8.90E-02	-0.01 7.36E-01	0.48 4.17E-08	CC
Remnant-C	Abdominal Obesity Class 2	*MPP7*	rs138618401	10	28433865	0.01	T/C	0.05 1.99E-01	-0.03 4.74E-01	0.68 1.82E-09	CC
Remnant-C	Abdominal Obesity Based on WHR	*BUD13*	rs2041967	11	116645149	0.42	G/A	-0.06 7.14E-34	-0.05 4.25E-10	-0.03 1.53E-02	EDGxE
Remnant-C	Abdominal Obesity Based on WHR	*APOA5*	rs7123666	11	116667083	0.14	A/G	0.09 2.19E-32	0.07 2.72E-10	0.03 2.59E-02	EDGxE

Supplemental Table S12. Genomic inflation factors observed in GWISs for quantitative TG levels

Trait	Environment		Marginal Model	Gene-by-Environment Interaction Model	
			Marginal	Main SNP	Interactive
TG	Obesity	Overweight Class 1	**1.050356***	0.926899	0.955029
		Overweight Class 2	1.047940	1.016899	1.006079
		Obesity	1.041676	1.039275	**1.065918***
	Abdominal Obesity	Abdominal Obesity Class 1	1.045046	1.040715	0.975952
		Abdominal Obesity Class 2	1.041676	**1.063475***	0.911091
		Abdominal Obesity Based on WHR	1.044564	0.968182	0.985151

*** Any inflated results over 1.05 are shown in bold type.**

Supplemental Table S13. Gene-by-lifestyle interactions on quantitative BP levels

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)	
SBP	Ever Drinking	*MVK*	rs11067592	12	110069190	0.04	T/G	-0.32 4.95E-01	0.73 2.39E-01	-2.50 9.31E-03	EDGxE
SBP	Ever Drinking	*MYL2*	rs12229654	12	111414461	0.14	G/T	-1.47 2.46E-06	-0.69 8.98E-02	-1.88 2.67E-03	EDGxE
SBP	Ever Drinking	*BRAP*	rs77684561	12	112061723	0.33	T/C	0.09 7.11E-01	-0.62 1.02E-01	1.21 1.34E-02	EDGxE
SBP	Ever Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	-1.18 2.84E-05	-0.57 1.16E-01	-1.43 1.34E-02	EDGxE
SBP	Current Drinking	*MYO1H*	rs11066562	12	109869385	0.04	A/G	-0.02 9.70E-01	0.87 1.20E-01	-2.25 1.23E-02	EDGxE
SBP	Current Drinking	*MYL2*	rs12229654	12	111414461	0.14	G/T	-1.41 5.12E-06	-0.84 2.83E-02	-1.64 1.05E-02	EDGxE
SBP	Heavy Drinking	*TSPAN5*	rs12501917	4	99686361	0.24	A/G	0.02 9.14E-01	-0.39 7.50E-02	3.67 1.75E-08	CC
SBP	Moderate Drinking	*RPH3A*	rs4767019	12	113289070	0.38	G/A	-0.60 1.02E-03	-0.84 5.04E-05	1.11 1.10E-02	EDGxE
SBP	Obesity	*RCN1*	rs7947403	11	31942033	0.38	A/G	0.43 3.72E-02	0.21 3.34E-01	5.94 4.11E-08	CC
SBP	Obesity	*CUX2*	rs2157876	12	111592380	0.50	G/T	0.71 7.35E-05	0.87 2.17E-06	-4.19 9.45E-06	DG2/H2
SBP	Obesity	*WDR72*	rs7169126	15	53627970	0.10	A/G	-0.28 3.44E-01	-0.57 5.70E-02	9.23 3.40E-08	CC
SBP	Abdominal Obesity Class 1	*RIMS2*	rs193061272	8	104545906	0.05	G/A	-0.25 5.54E-01	1.74 1.16E-03	-4.93 5.00E-09	CC
SBP	Abdominal Obesity Class 1	*RIMS2*	rs4333556	8	104746639	0.06	C/T	-0.33 3.87E-01	1.40 4.93E-03	-4.33 3.06E-08	CC

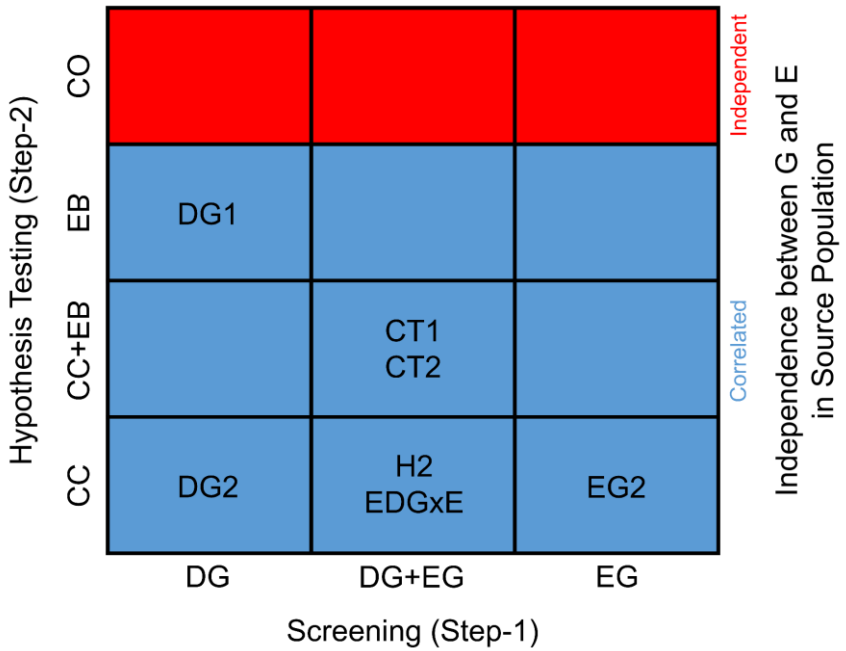
Supplemental Table S13. Continued

Trait	Environment	Gene	Marker	CHR	Position	MAF	A1/A2	GWAS	GxE Interaction		Test
								Marginal (*p*-value)	Main SNP (*p*-value)	Interactive (*p*-value)	
DBP	Ever Drinking	*ARID5B*	rs11594640	10	63871857	0.21	A/G	0.56 5.56E-05	-0.10 6.47E-01	1.18 2.60E-05	DG2/H2
DBP	Ever Drinking	*MYL2*	rs7957842	12	111363528	0.46	G/T	0.07 5.45E-01	-0.43 2.39E-02	0.86 5.56E-04	EDGxE
DBP	Ever Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	-0.72 6.53E-05	-0.30 1.91E-01	-0.98 7.58E-03	EDGxE
DBP	Current Drinking	*PDE7B*	rs9321532	6	136112216	0.41	G/A	0.44 9.92E-05	0.90 1.39E-08	-0.92 5.33E-05	DG2
DBP	Current Drinking	*ARID5B*	rs11594640	10	63871857	0.21	A/G	0.56 5.16E-05	-0.01 9.43E-01	1.18 2.42E-05	DG2/H2
DBP	Current Drinking	*MYO1H*	rs11066556	12	109866817	0.04	T/C	0.02 9.57E-01	0.58 1.00E-01	-1.43 1.14E-02	EDGxE
DBP	Current Drinking	*MYL2*	rs7957842	12	111363528	0.46	G/T	0.05 6.61E-01	-0.35 4.47E-02	0.79 1.28E-03	EDGxE
DBP	Current Drinking	*OAS3*	rs2072134	12	113409176	0.11	A/G	-0.68 1.60E-04	-0.32 1.52E-01	-1.05 5.64E-03	EDGxE
DBP	Moderate Drinking	*RPH3A*	rs4767019	12	113289070	0.38	G/A	-0.39 8.86E-04	-0.52 7.65E-05	0.62 2.62E-02	EDGxE

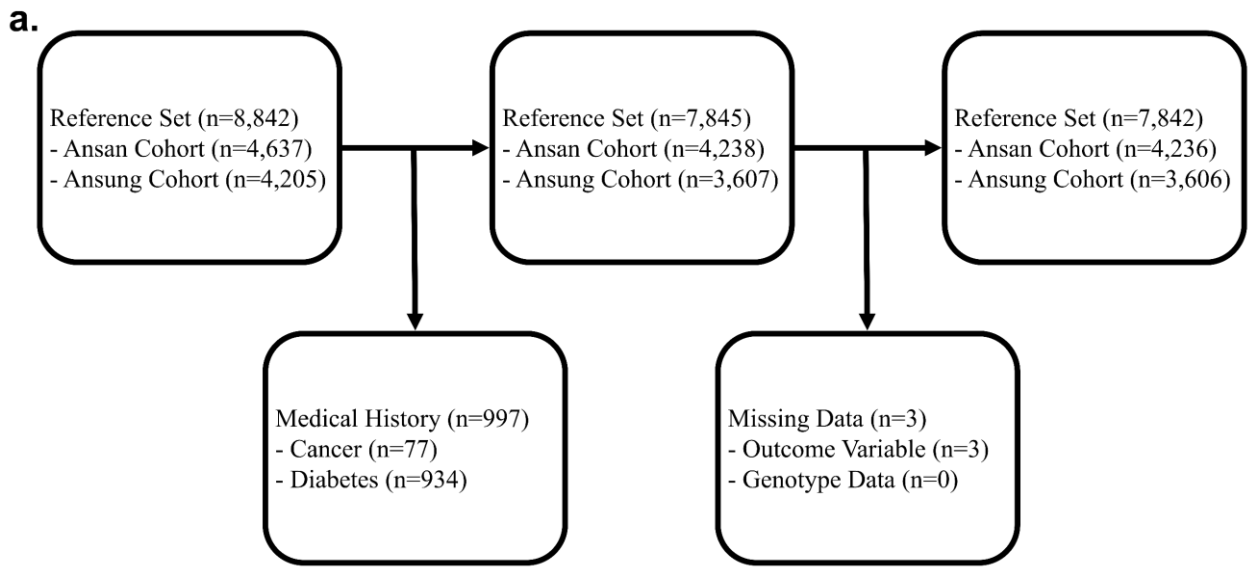
Supplemental Table S14. Genomic inflation factors observed in GWISs for quantitative SBP levels

Trait	Environment		Marginal Model	Gene-by-Environment Interaction Model	
			Marginal	Main SNP	Interactive
SBP	Cigarette Smoking	Ever Smoking	**1.062499***	**1.060062***	0.979165
		Current Smoking	**1.062987***	1.048906	1.016427
	Alcohol Consumption	Ever Drinking	**1.061524***	**1.093064***	1.025902
		Current Drinking	**1.062011***	**1.093064***	1.007954
		Moderate Drinking	**1.061036***	**1.079181***	0.943794
		Low-Risk Drinking	**1.060549***	1.047940	1.022578
		Heavy Drinking	**1.062011***	1.045046	1.014068
		Binge Drinking	**1.062987***	**1.060062***	0.968182
	Obesity	Underweight	**1.057629***	**1.057143***	**1.105071***
		Overweight Class 1	**1.050840***	0.997204	0.975952
		Overweight Class 2	**1.061524***	1.000467	1.034484
		Obesity	**1.065918***	**1.059089***	**1.306686***
	Abdominal Obesity	Abdominal Obesity Class 1	**1.064940***	0.983767	1.037836
		Abdominal Obesity Class 2	**1.068365***	1.017844	**1.192466***
		Abdominal Obesity Based on WHR	**1.064452***	0.929995	0.960003

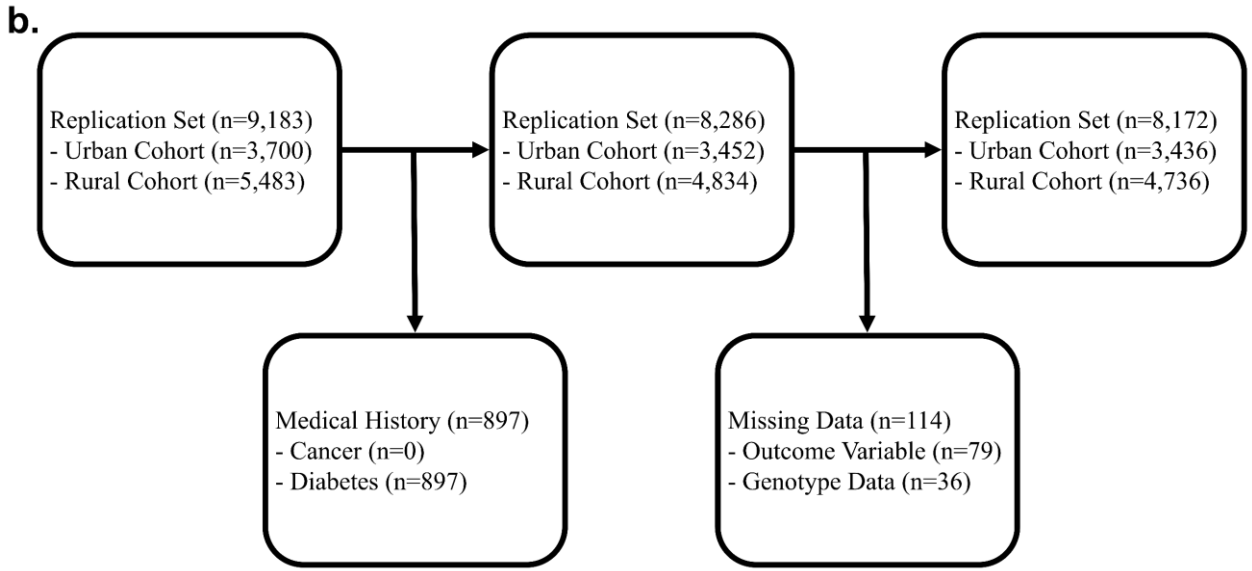
*** Any inflated results over 1.05 are shown in bold type.**



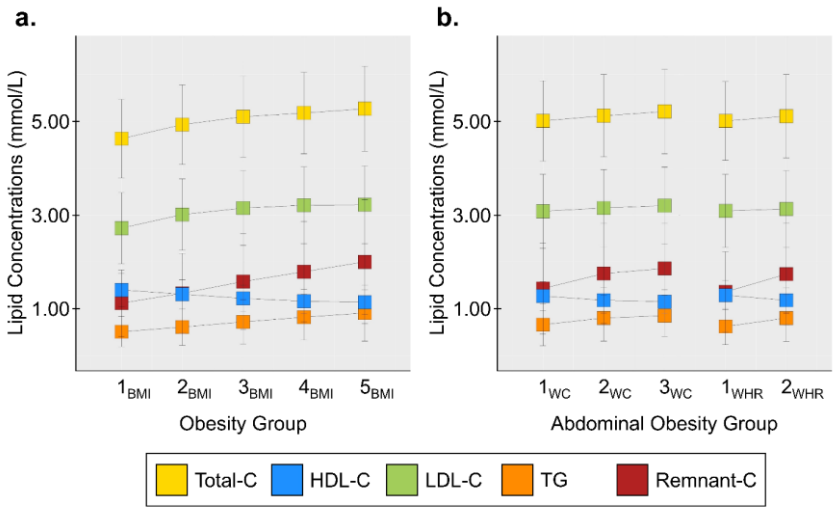
Supplemental Figure S1. Analytical models categorized by underlying assumptions and methods for screening (step-1) and hypothesis testing (step-2). We categorized analytical approaches for testing GxEs, such as exhaustive scans and two-step methods, by 1) the assumption of independence between genetic and environmental factors, 2) methods for screening (step-1), and methods for hypothesis testing (step-2).



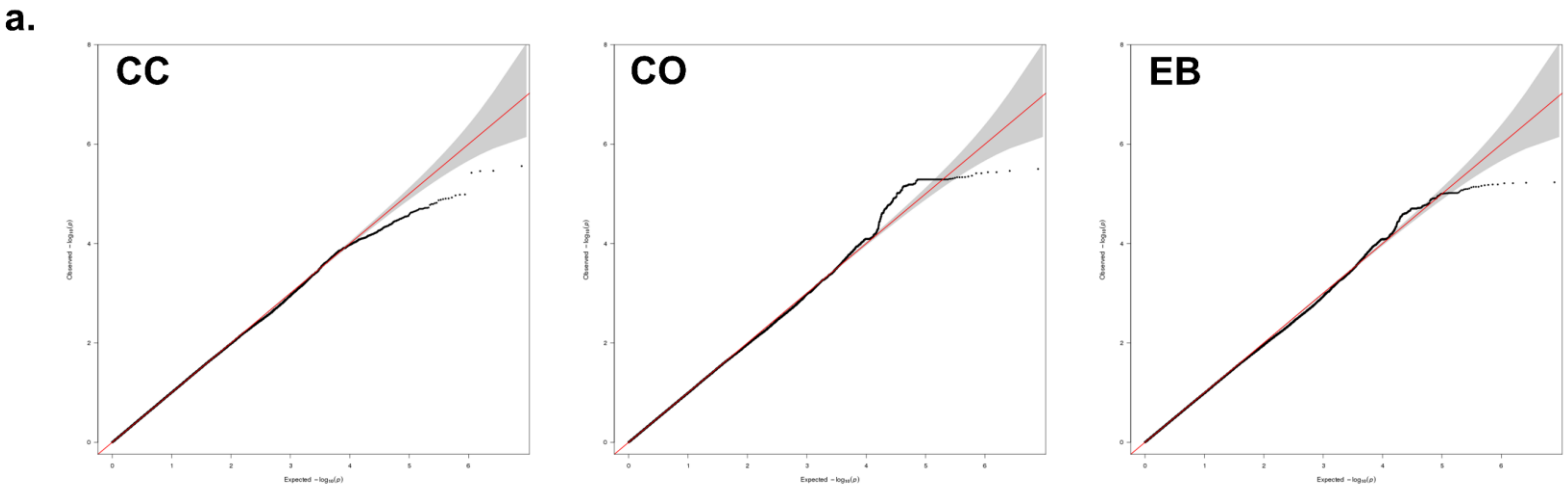
Supplemental Figure S2. Flow chart of inclusion and exclusion criteria for the study on dyslipidemia. We excluded individuals who have suffered cancer or diabetes from this study. We considered people taking any kind of lipid-lowering drug as dyslipidemia patients: 1) 95 people for the Ansan cohort, 2) 73 people for the Ansung cohort, 3) 83 people for the urban cohort, and 4) 9 people for the rural cohort. (a) Flow chart of inclusion and exclusion criteria for the reference set. (b) Flow chart of inclusion and exclusion criteria for the replication set.



Supplemental Figure S2. Continued

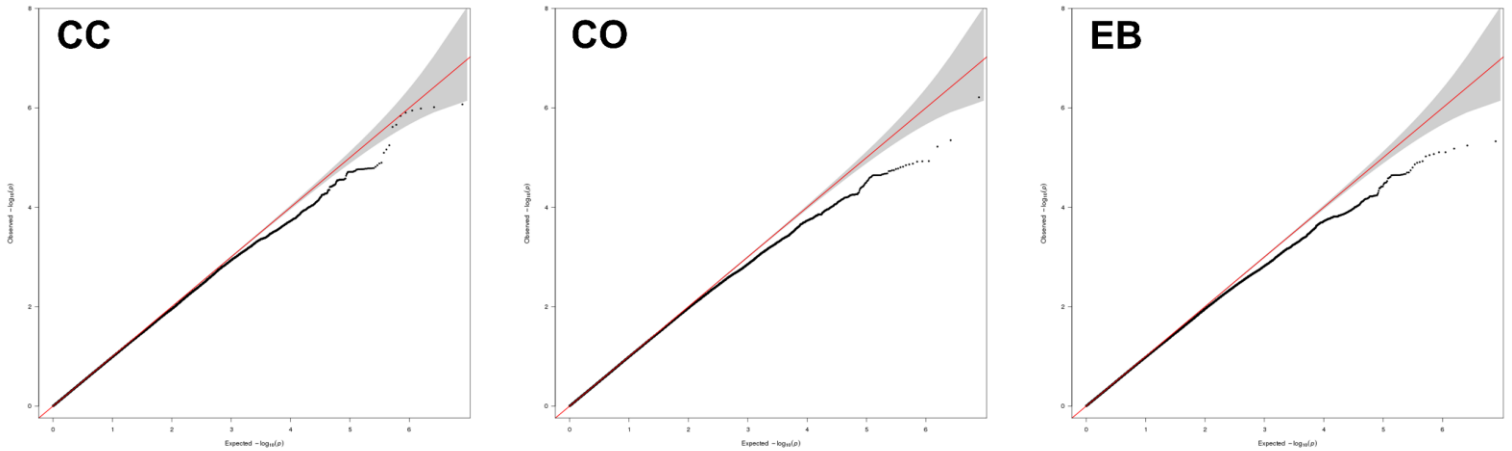


Supplemental Figure S3. Trends of plasma lipid levels stratified into subgroups for obesity traits based on BMI, WC, and WHR. Figure (a) shows trends of plasma lipids stratified into subgroups for obesity traits based on BMI: group 1_{BMI} (BMI<18.5 kg/m^2), 2_{BMI} (18.5≤BMI<23.0 kg/m^2), 3_{BMI} (23.0≤BMI<25.0 kg/m^2), 4_{BMI} (25.0≤BMI<30.0 kg/m^2), and 5_{BMI} (30.0 kg/m^2≤BMI). Figure (b), on the other hand, described lipid trends stratified into subgroups for abdominal obesity traits based on WC or WHR: group 1_{WC} (WC≤90 cm for males, 80 cm for females), 2_{WC} (WC>90 cm for males, 80 cm for females), 3_{WC} (WC>102 cm for males, 88 cm for females), and 1_{WHR} (WHR≤0.90 for males, 0.85 for females), 2_{WHR} (WHR>0.90 for males, 0.85 for females). Further details are presented in Supplemental Table S2 and S3.



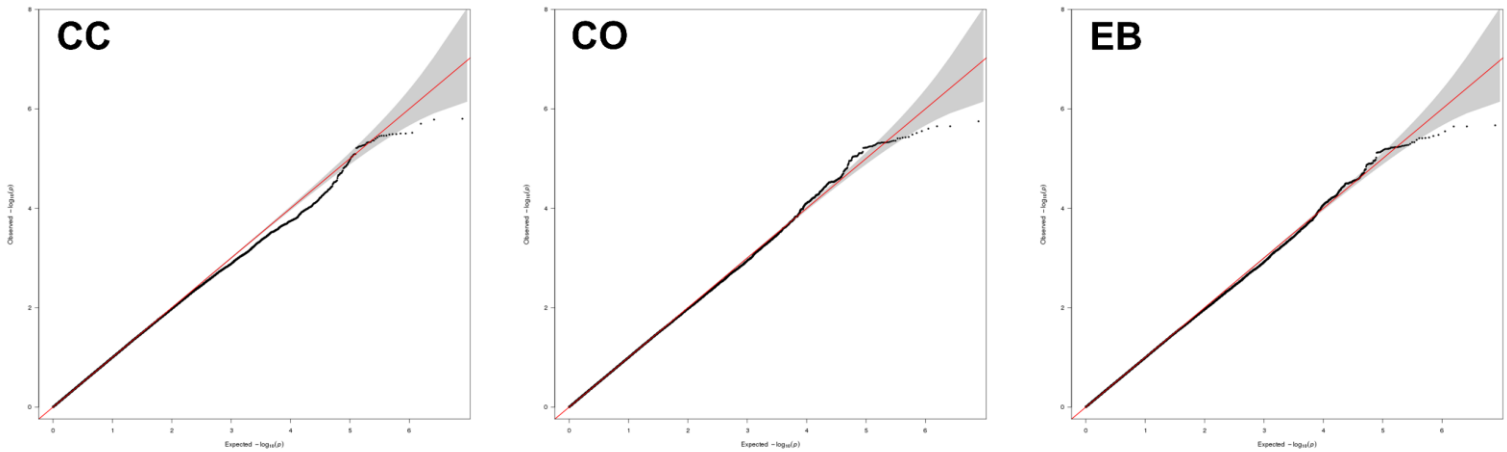
Supplemental Figure S4. Quantile-Quantile plots for gene-by-obesity interactions on Total-C. We have drawn quantile-quantile plots for genetic interactions with obesity traits on the risk of abnormal Total-C elevation. (a) Plots for genetic interactions with BMI. (b) Plots for gene-by-WC interactions. (c) Plots for genetic interactions with WHR.

b.



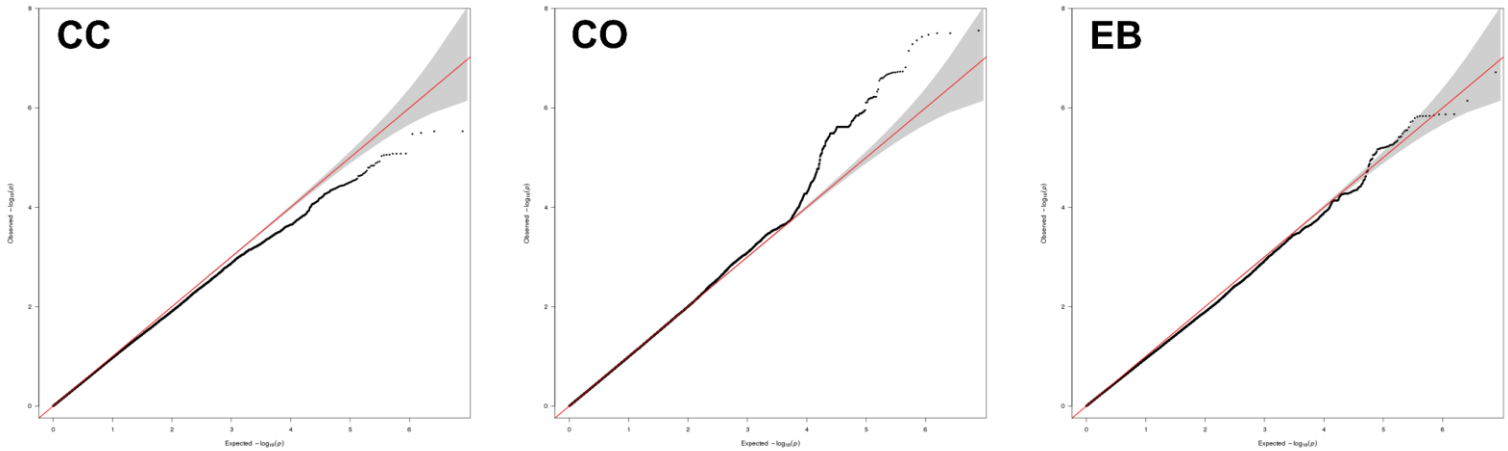
Supplemental Figure S4. Continued

c.



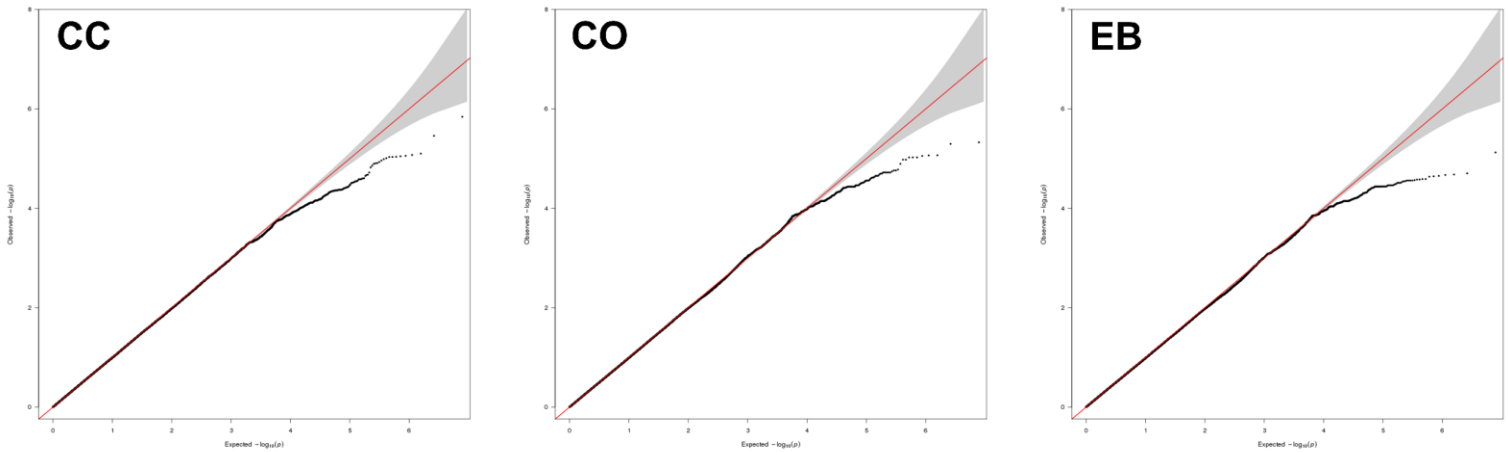
Supplemental Figure S4. Continued

a.



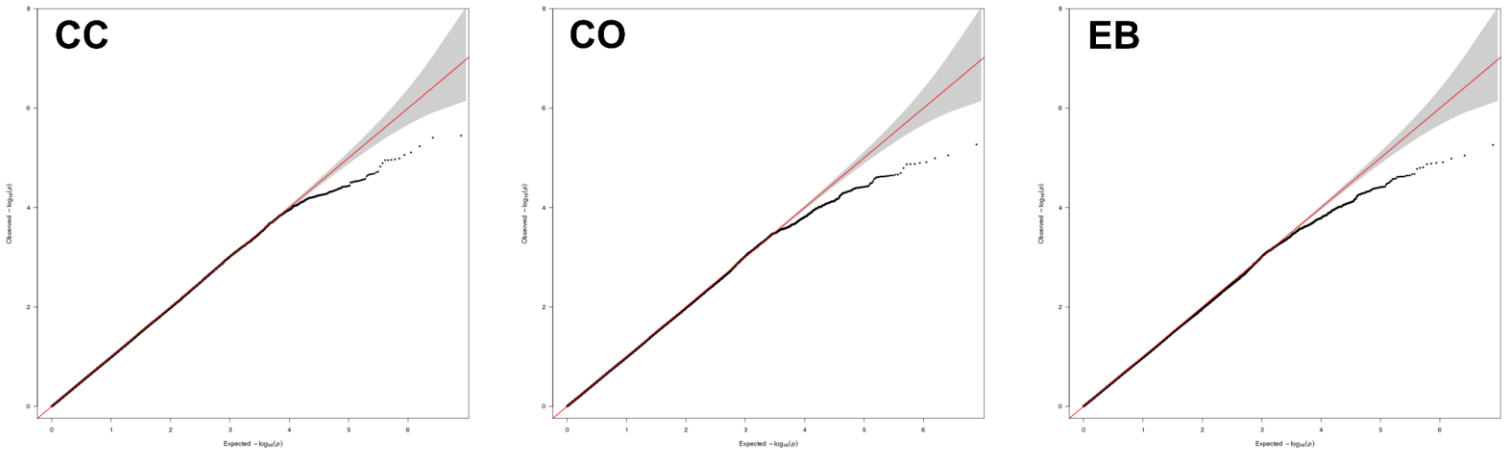
Supplemental Figure S5. Quantile-Quantile plots for gene-by-obesity interactions on HDL-C. We have drawn quantile-quantile plots for genetic interactions with obesity traits on the risk of abnormal HDL-C reduction. (a) Plots for genetic interactions with BMI.

a.



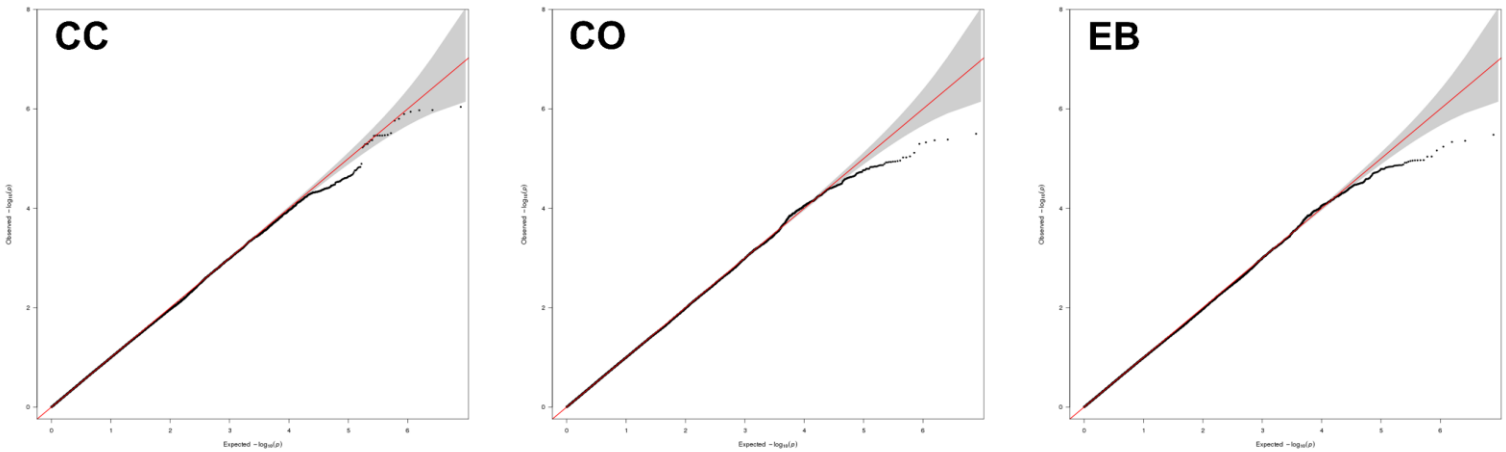
Supplemental Figure S6. Quantile-Quantile plots for gene-by-obesity interactions on LDL-C. We have drawn quantile-quantile plots for genetic interactions with obesity traits on the risk of abnormal LDL-C elevation. (a) Plots for genetic interactions with BMI. (b) Plots for gene-by-WC interactions. (c) Plots for genetic interactions with WHR.

b.



Supplemental Figure S6. Continued

c.



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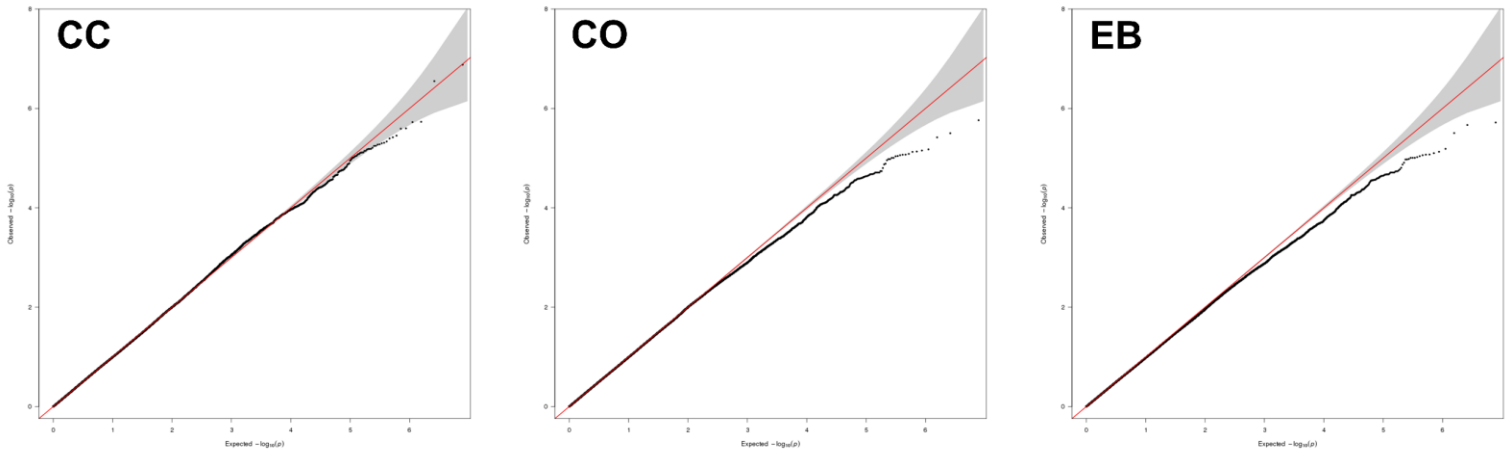
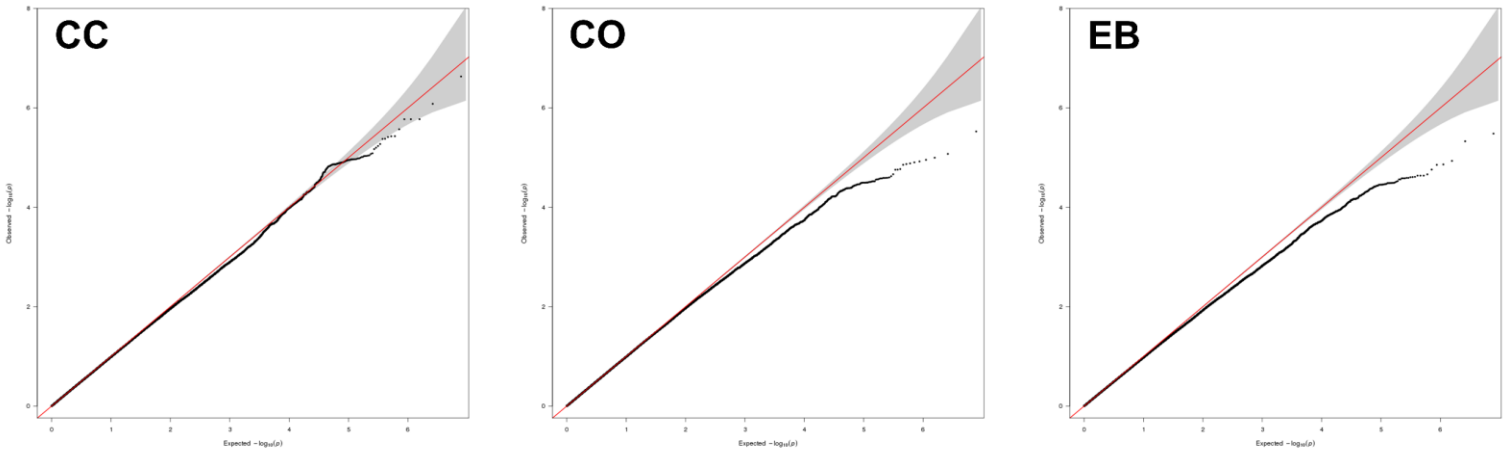
a.



Supplemental Figure S7. Quantile-Quantile plots for gene-by-obesity interactions on TG. We illustrated quantile-quantile plots for genetic interactions with obesity traits on the risk of abnormal TG elevation. (a) Plots for genetic interactions with BMI. (b) Plots for genetic interactions with WC. (c) Plots for genetic interactions with WHR.

b.



Supplemental Figure S7. Continued

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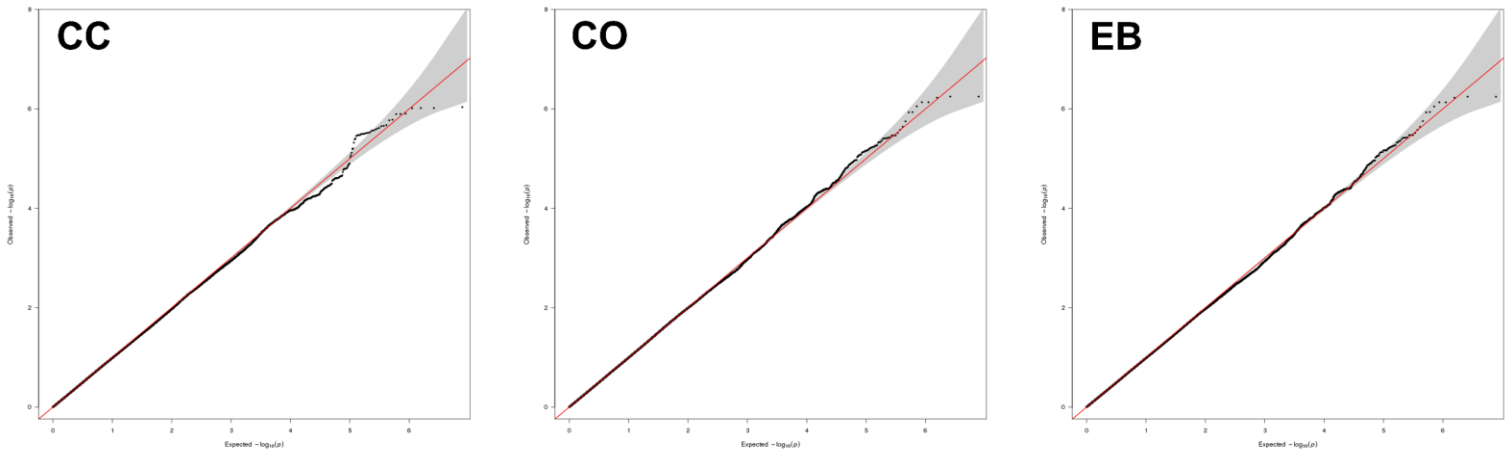

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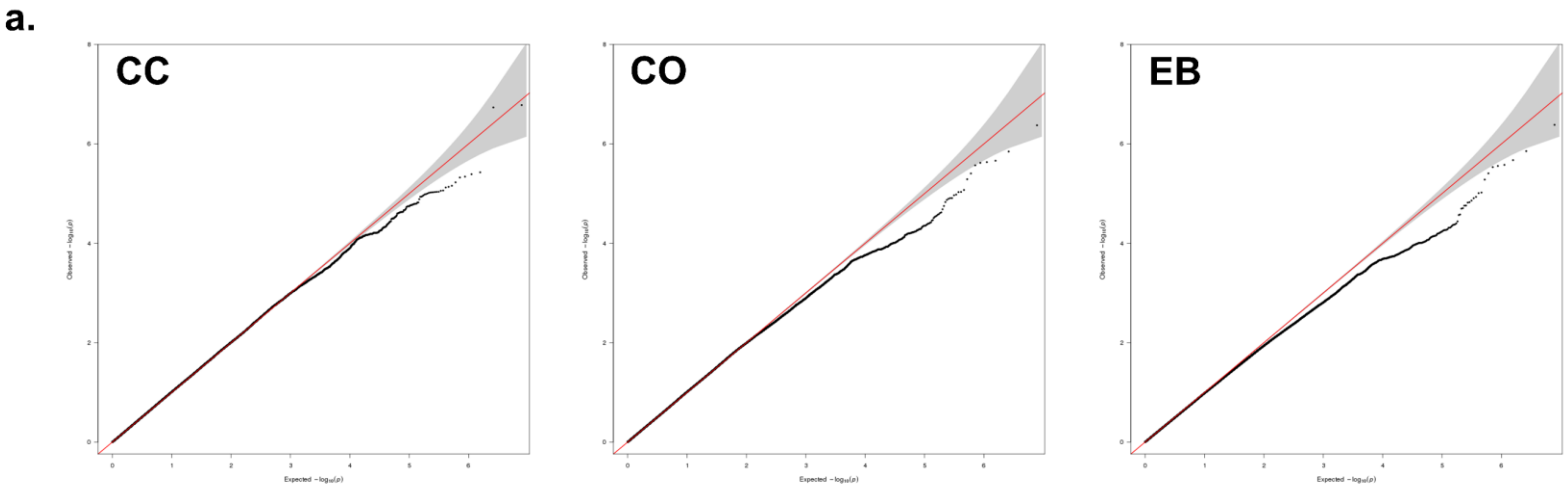
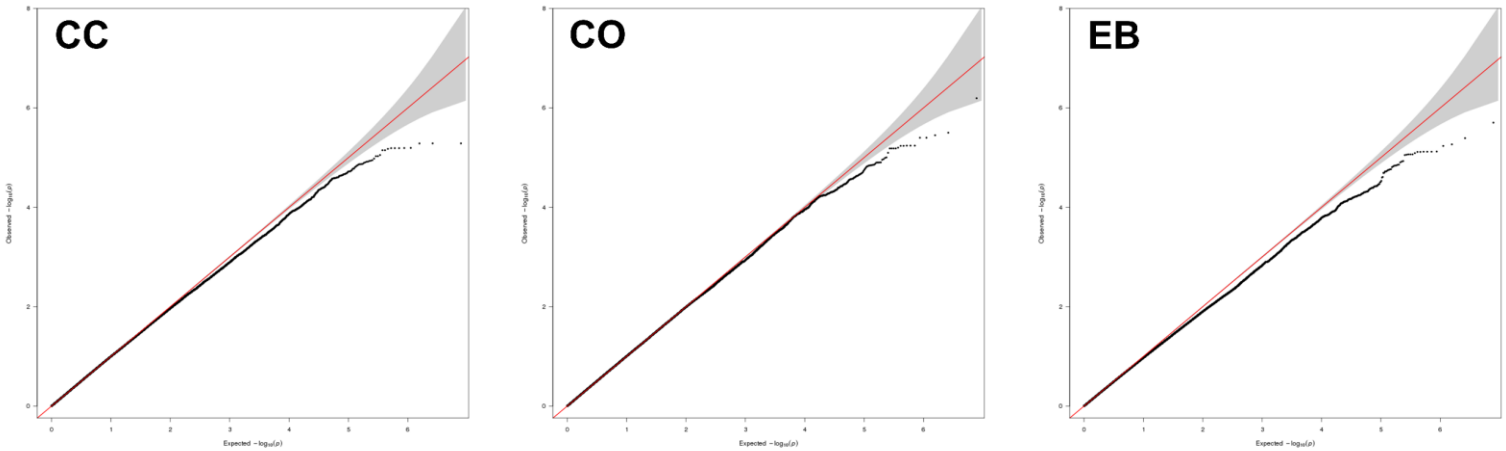


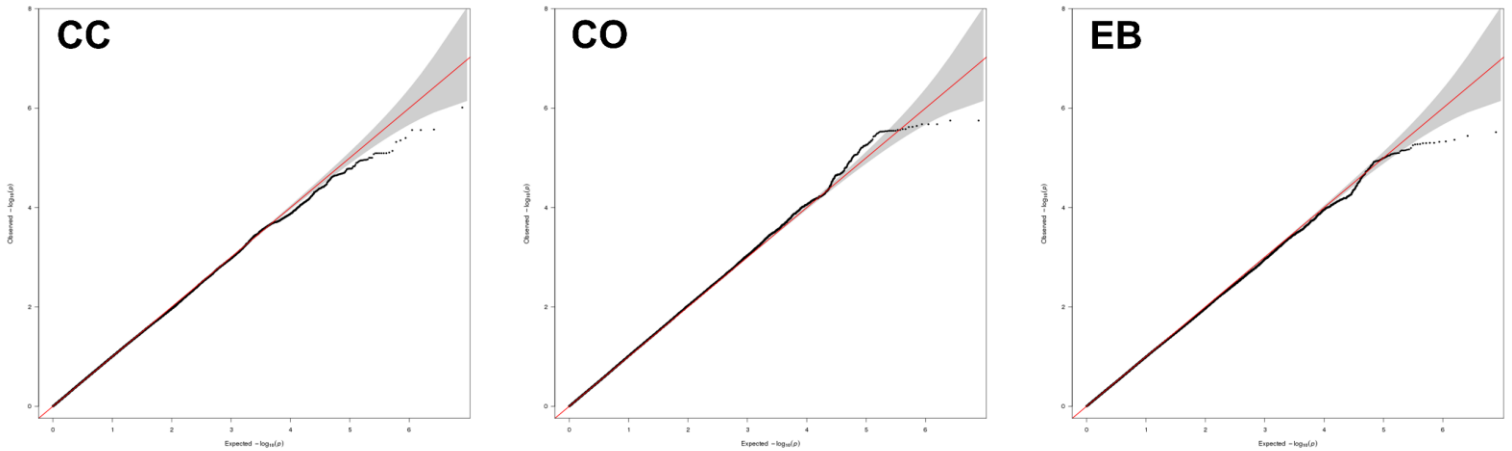
Supplemental Figure S8. Quantile-Quantile plots for gene-by-obesity interactions on Remnant-C. We have drawn quantile-quantile plots for gene-by-obesity interactions on the risk of abnormal elevation of Remnant-C. (a) Plots for genetic interactions with BMI. (b) Plots for gene-by-WC interactions. (c) Plots for genetic interactions with WHR.

b.



Supplemental Figure S8. Continued

c.



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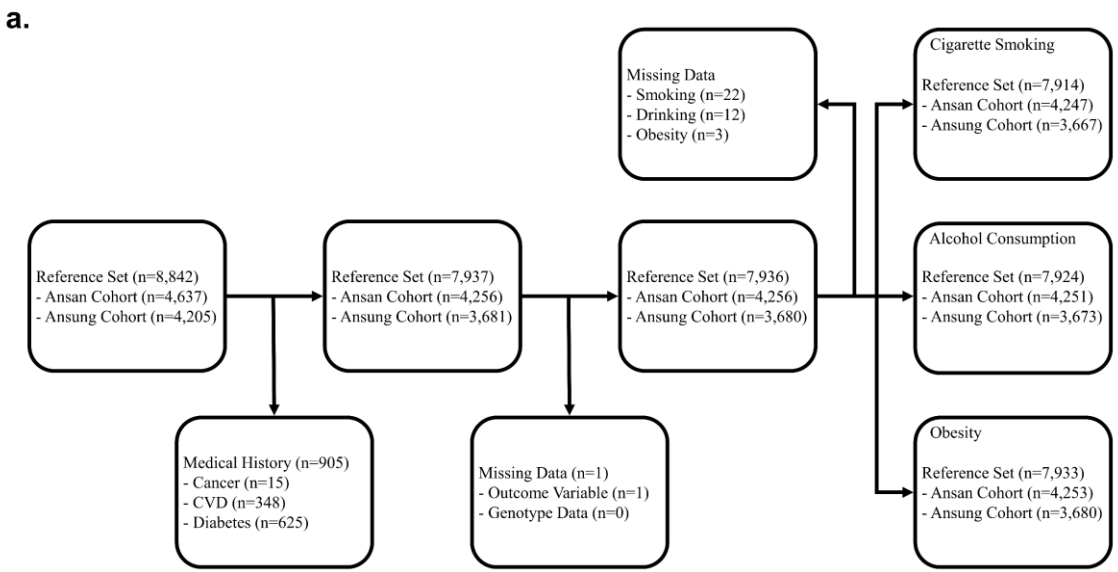
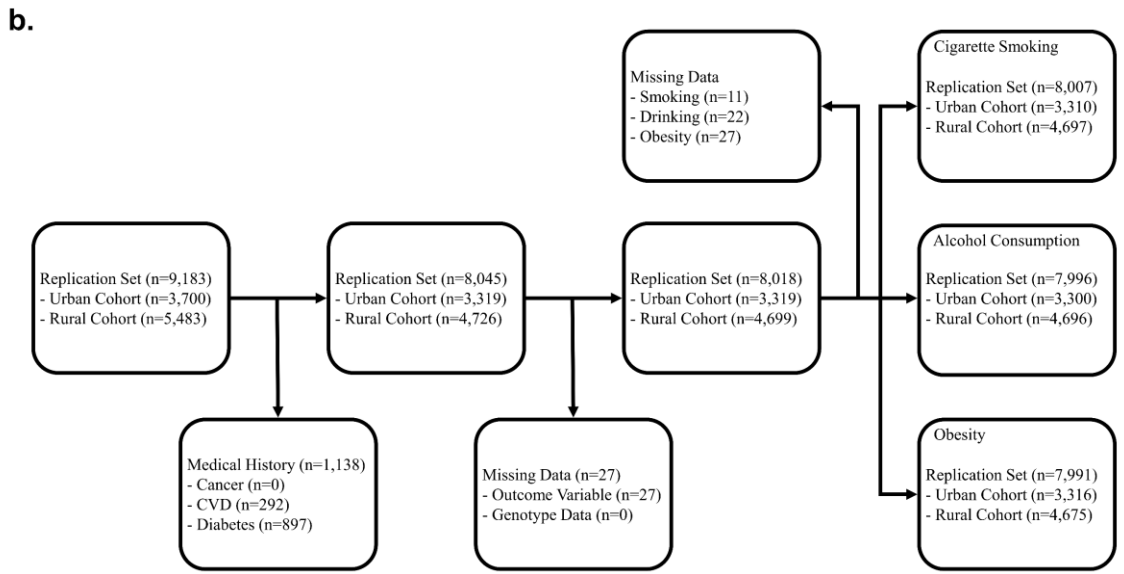


Supplemental Figure S9. Flow chart of inclusion and exclusion criteria for the study on hypertension. We excluded individuals who have suffered cancer or diabetes or any CVDs from this study. We considered people taking any antihypertensive drugs as hypertension patients: 1) 118 people for the Ansan cohort, 2) 650 people for the Ansung cohort, 3) 376 people for the urban cohort, and 4) 30 people for the rural cohort. (a) Flow chart of inclusion and exclusion criteria for the reference set. (b) Flow chart of inclusion and exclusion criteria for the replication set.



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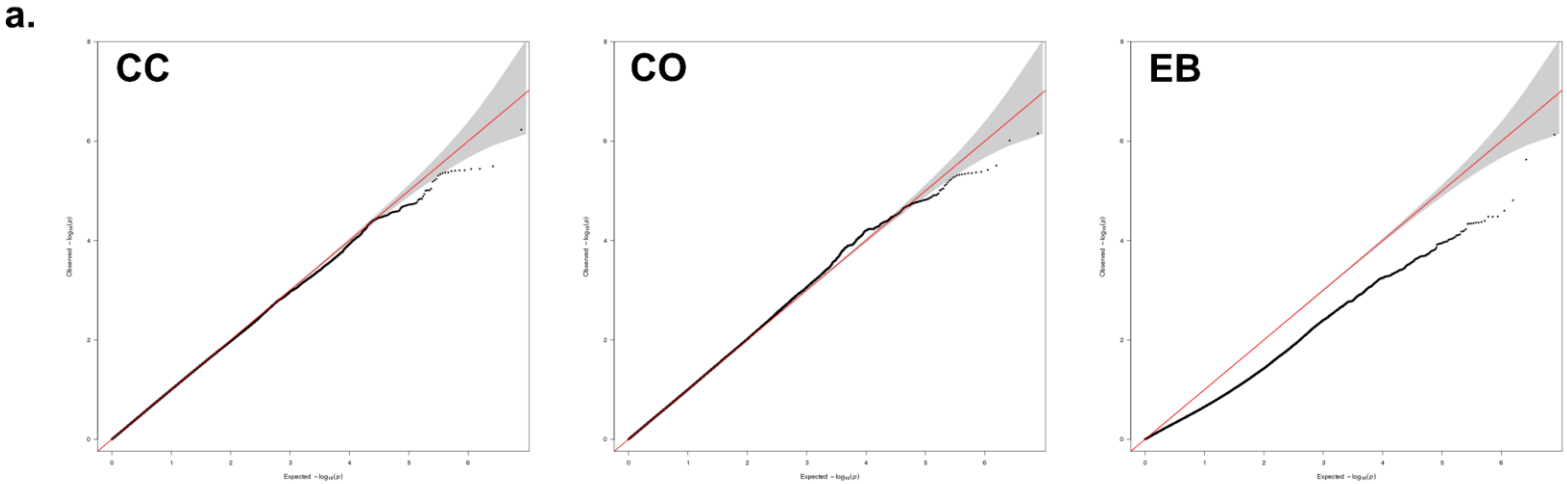
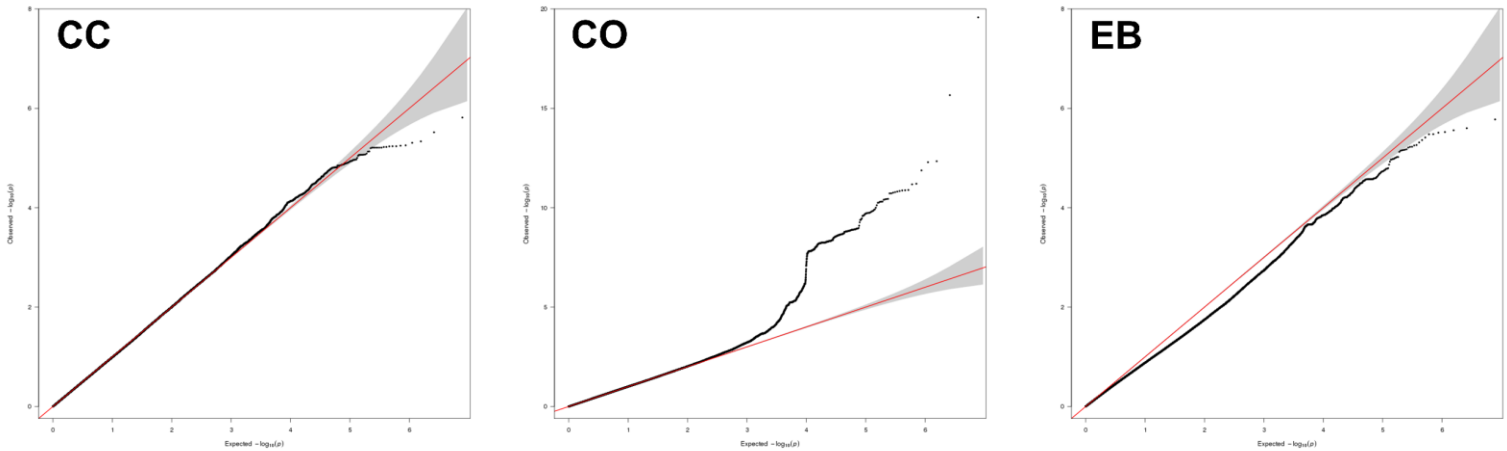


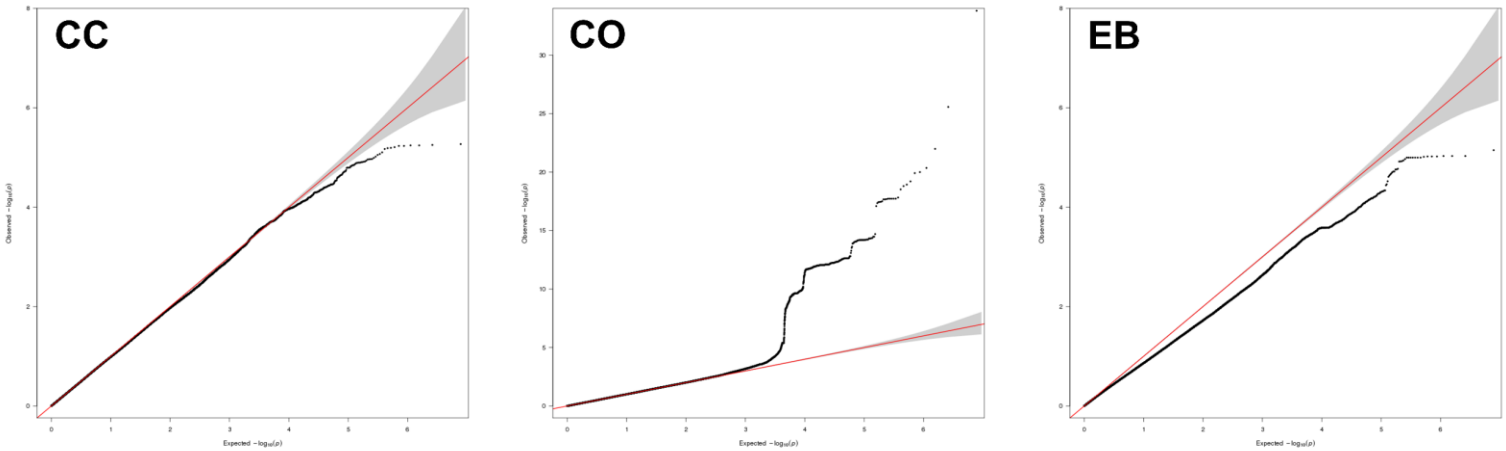
Supplemental Figure S10. Quantile-Quantile plots for gene-by-lifestyle interactions on HBP-S1. We illustrated quantile-quantile plots for genetic interactions with lifestyle factors on the risk of HBP-S1. (a) Plots for genetic interactions with ever smoking on the risk of HBP-S1. (b) Plots for genetic interactions with low-risk drinking on the risk of HBP-S1. (c) Plots for genetic interactions with heavy drinking on the risk of HBP-S1. (d) Plots for genetic interactions with moderate drinking on the risk of HBP-S1. (e) Plots for genetic interactions with binge drinking on the risk of HBP-S1.

b.



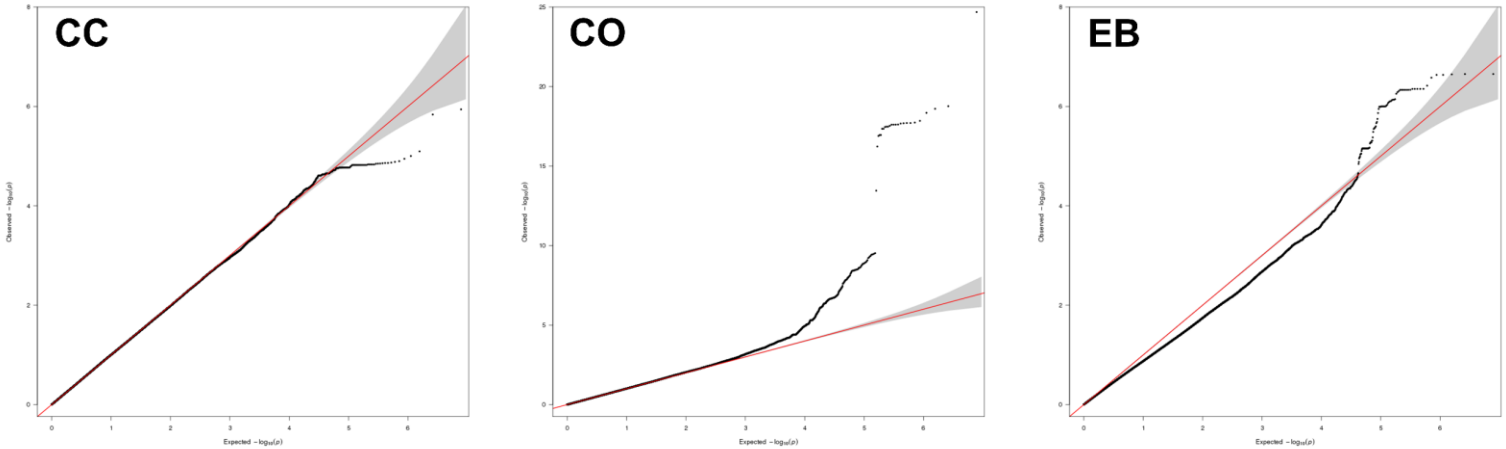
Supplemental Figure S10. Continued

c.



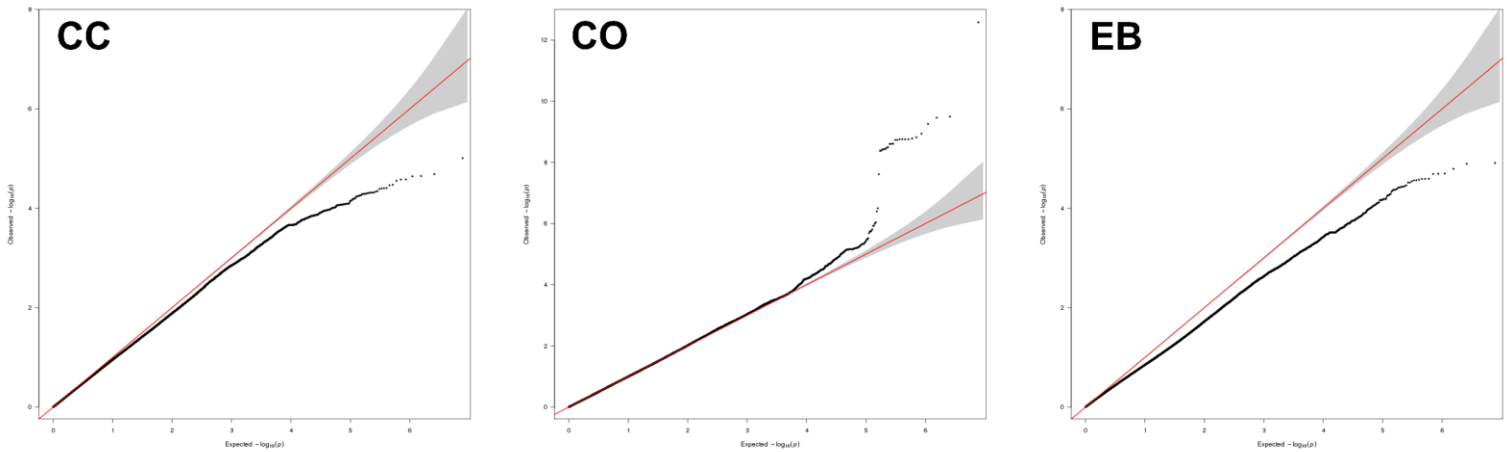
Supplemental Figure S10. Continued

d.



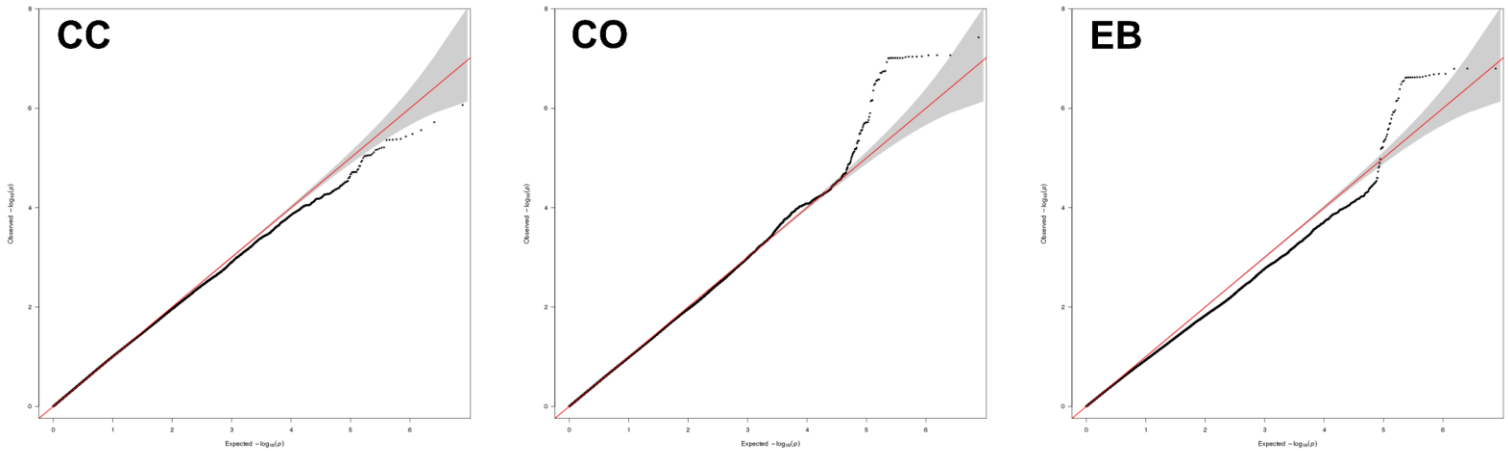
Supplemental Figure S10. Continued

e.



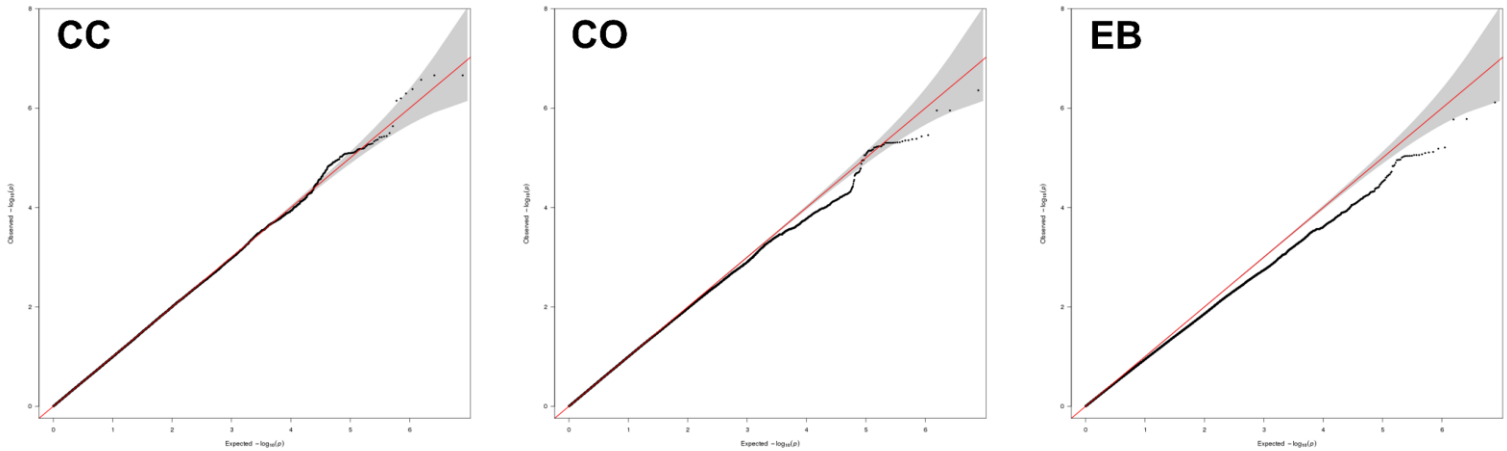
Supplemental Figure S10. Continued

a.



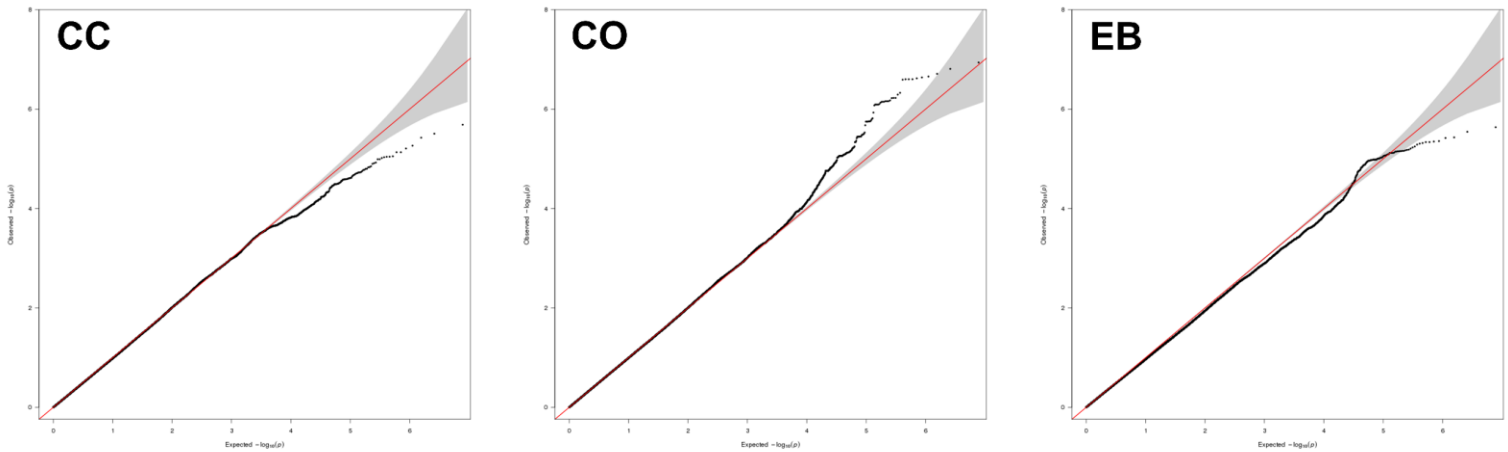
Supplemental Figure S11. Quantile-Quantile plots for gene-by-lifestyle interactions on HBP-S2. We illustrated quantile-quantile plots for genetic interactions with lifestyle factors on the risk of HBP-S2. (a) Plots for genetic interactions with obesity on the risk of HBP-S2. (b) Plots for genetic interactions with abdominal obesity class 1 on the risk of HBP-S2. (c) Plots for genetic interactions with abdominal obesity decided by using WHR on the risk of HBP-S2.

b.

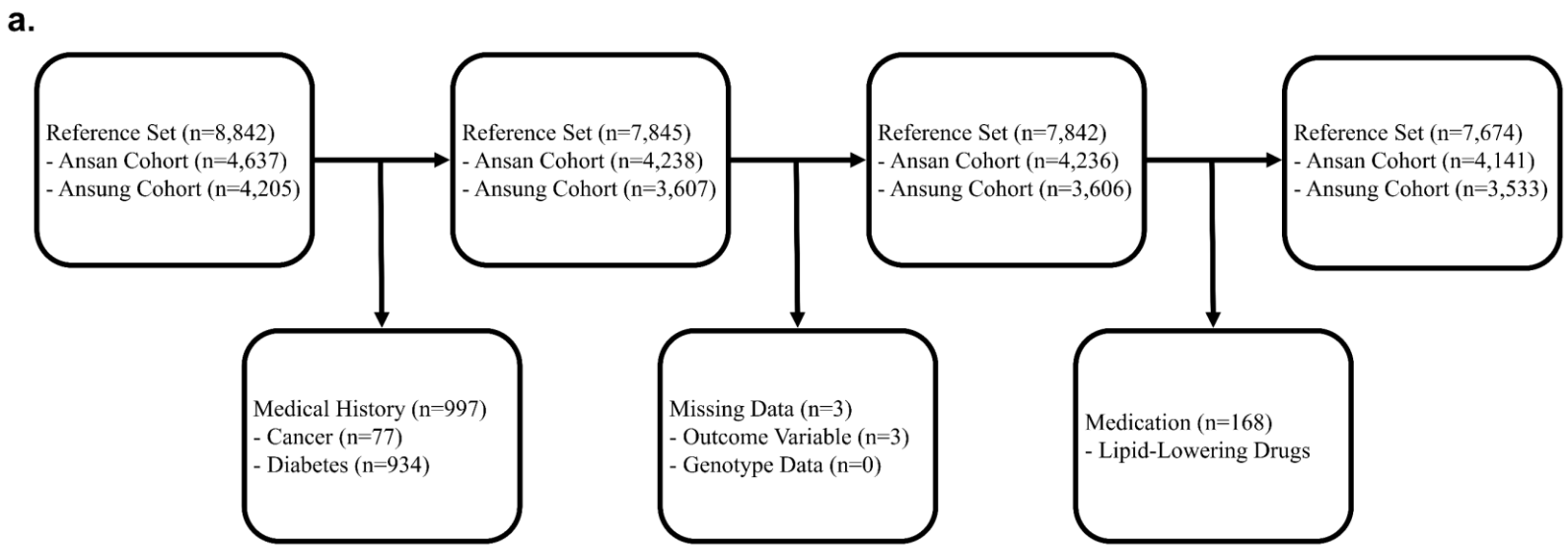


Supplemental Figure S11. Continued

c.

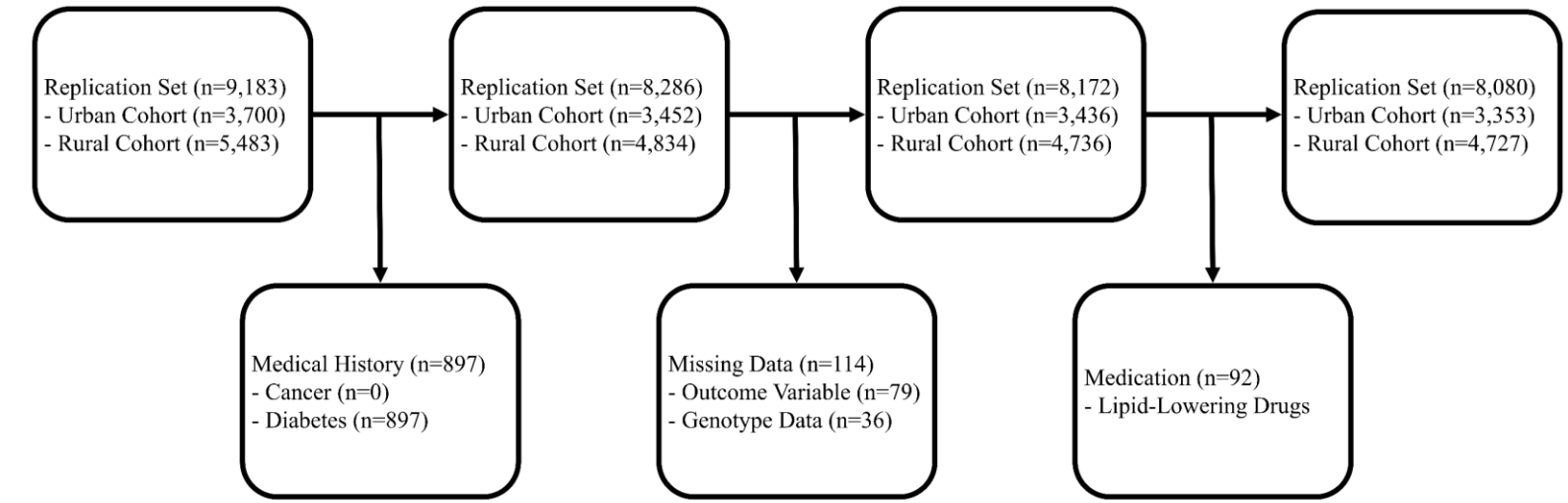


Supplemental Figure S11. Continued

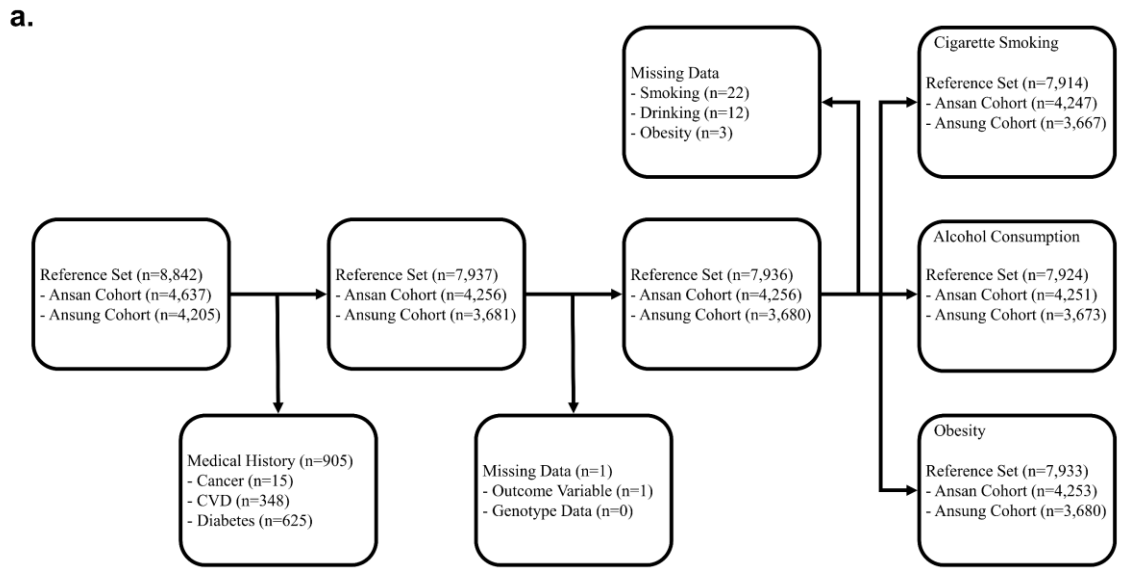


Supplemental Figure S12. Flow chart of inclusion and exclusion criteria for the study on continuous lipid levels. We excluded individuals who have suffered cancer or diabetes from this study. We also excluded people taking any kind of lipid-lowering medication: 1) 95 people for the Ansan cohort, 2) 73 people for the Ansung cohort, 3) 83 people for the urban cohort, and 4) 9 people for the rural cohort. (a) Flow chart of inclusion and exclusion criteria for the reference set. (b) Flow chart of inclusion and exclusion criteria for the replication set.

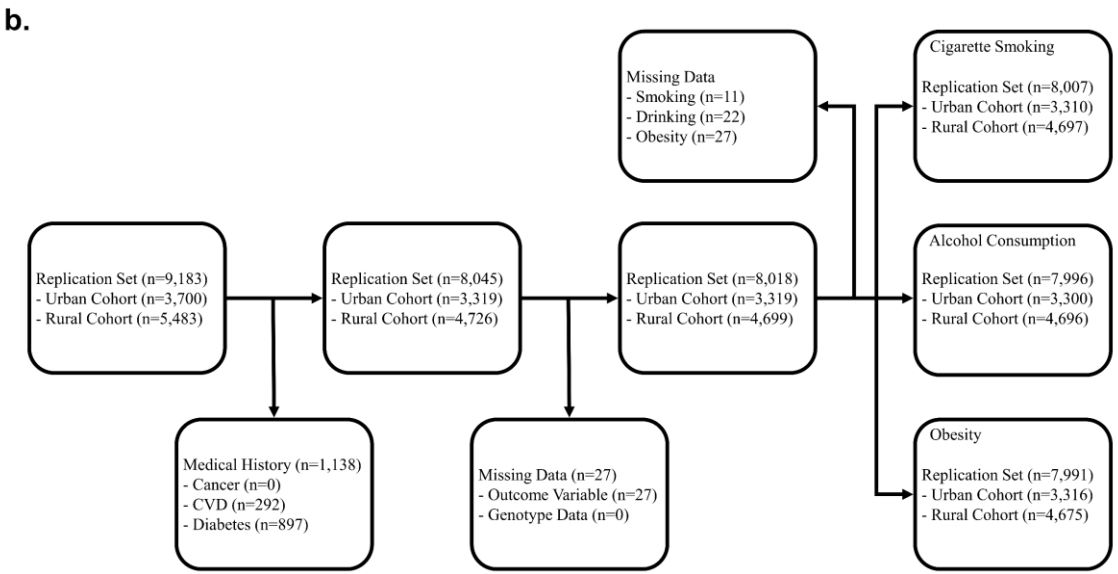
b.



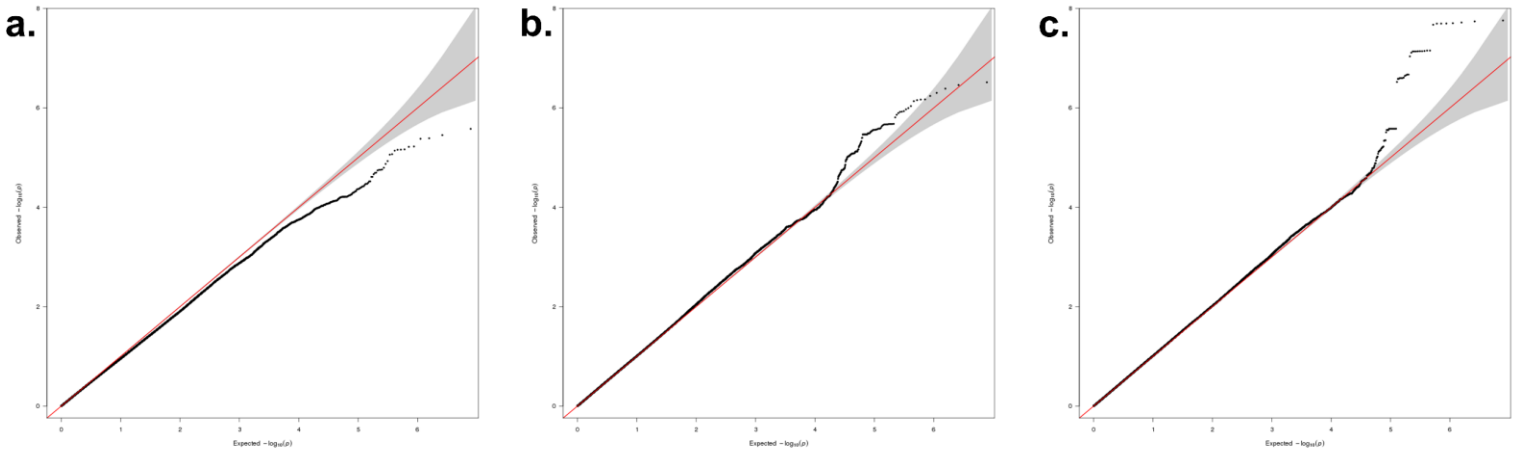
Supplemental Figure S12. Continued



Supplemental Figure S13. Flow chart of inclusion and exclusion criteria for the study on continuous BP levels. We excluded people who have suffered cancer or diabetes or CVD from this study. We added 10 mmHg and 5 mmHg to observed SBP and DBP levels, respectively, for people taking any antihypertensive drugs: 1) 118 people for the Ansan cohort, 2) 650 people for the Ansung cohort, 3) 376 people for the urban cohort, and 4) 30 people for the rural cohort. (a) Flow chart for the reference set. (b) Flow chart for the replication set.



Supplemental Figure S13. Continued



Supplemental Figure S14. Quantile-Quantile plots for interactions on quantitative scales of TG and SBP. We illustrated quantile-quantile plots for genetic interactions with environmental factors on quantitative scales of outcome variables. (a) Plots for genetic interactions with BMI on quantitative TG scales. (b) Plots for genetic interactions with low-risk drinking on quantitative SBP scales. (c) Plots for genetic interactions with heavy drinking on quantitative SBP scales.

Reference Table R1. Type 1 error rates for GxE tests across several models and methods

	Exhaustive scans			Two-step methods				
Model	CC	CO	EB	DG|EB	EG|G×E	H2	Cocktail	EDG×E
Base[a]	0.041	0.057	0.046	0.046	0.052	0.045	0.048	0.045
Population G–E association[b]								
10 SNPs	0.042	>0.999	0.042	0.048	0.048	0.045	0.050	0.046
50 SNPs	0.042	>0.999	0.048	0.045	0.044	0.048	0.046	0.051
G–D association[c]								
10 SNPs	0.039	0.037	0.038	0.042	0.046	0.047	0.044	0.048
Both G–E and G–D associations								
10 G–E SNPs, 10 G–D SNPs	0.049	>0.999	0.046	0.040	0.048	0.042	0.048	0.050
50 G–E SNPs, 10 G–D SNPs	0.049	>0.999	0.046	0.043	0.046	0.048	0.044	0.049

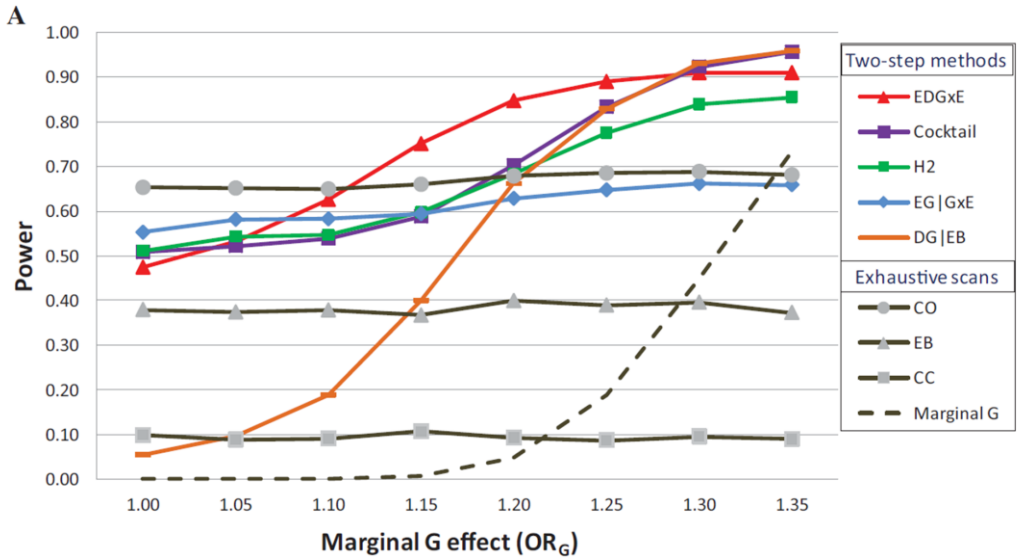
Each estimate of type 1 error rate is based on the proportion of 2,000 replicate datasets for which the indicated procedure identified at least one statistically significant result among 999,999 non-disease susceptibility variants. [a]The base model has no variants with DG associations or EG correlations. [b]Number of non-disease susceptibility variants simulated to have EG correlations in a source population. [c]Number of non-disease susceptibility variants simulated to have DG associations (but no GxEs).

Reference Table R2. Power of detect the disease susceptibility locus across a range of models and methods

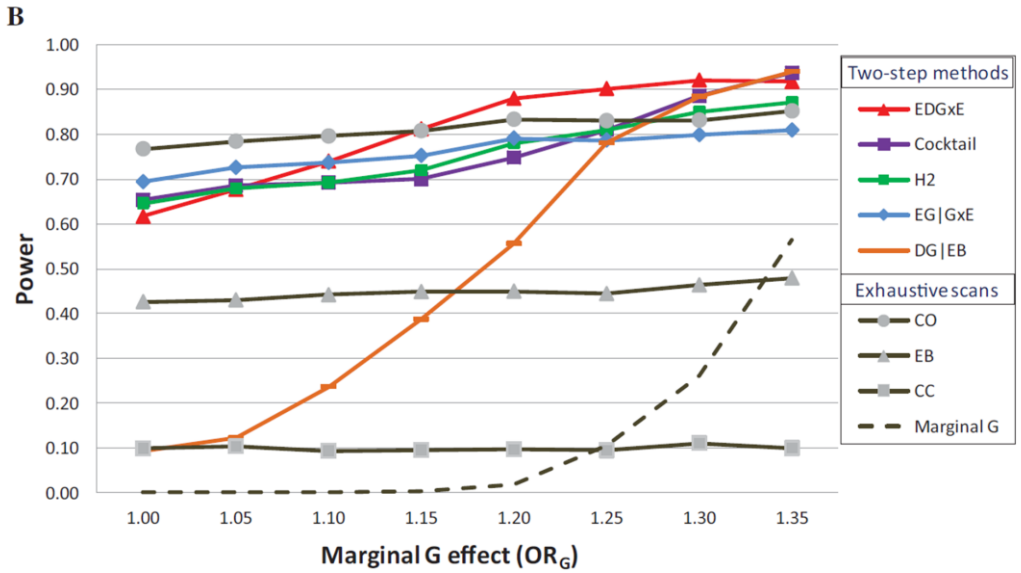
	Exhaustive scans			Two-step methods				
Model[a]	CC	CO	EB	DG|EB	EG|G×E	H2	Cocktail	EDG×E
Base[b]	0.093	0.679	0.400	0.662	0.629	0.683	0.703	**0.847**
q_A								
0.15	0.051	0.523	0.259	0.518	0.473	0.521	0.563	**0.727**
0.30	0.100	0.661	0.381	0.654	0.608	0.676	0.711	**0.845**
p_E								
0.25	0.036	0.474	0.233	0.546	0.412	0.499	0.565	**0.698**
0.50	0.098	0.675	0.388	0.668	0.621	0.686	0.717	**0.839**
Marginal OR_E								
1.5	0.097	0.689	0.381	0.657	0.693	0.724	0.732	**0.856**
1.8	0.106	0.666	0.382	0.626	0.710	0.714	0.707	**0.852**
Bin size (B)								
10	0.096	0.666	0.380	0.669	0.613	0.673	0.716	**0.811**
20	0.099	0.681	0.372	0.688	0.626	0.662	0.733	**0.800**
DSL–E association[c]								
$OR_{DSL-E} = 0.8$	0.086	0.003	0.031	0.234	0.004	**0.309**	0.190	0.258
$OR_{DSL-E} = 1.2$	0.084	**0.999**	0.151	0.568	0.908	0.867	0.705	0.908
G–E association[d]								
10 SNPs	0.097	NA	0.365	0.654	0.558	0.630	0.678	**0.747**
50 SNPs	0.093	NA	0.394	**0.648**	0.435	0.547	0.553	0.600
G–D association[e]								
10 SNPs	0.088	0.683	0.400	0.638	0.626	0.681	0.694	**0.831**

Reference Table R2. Continued

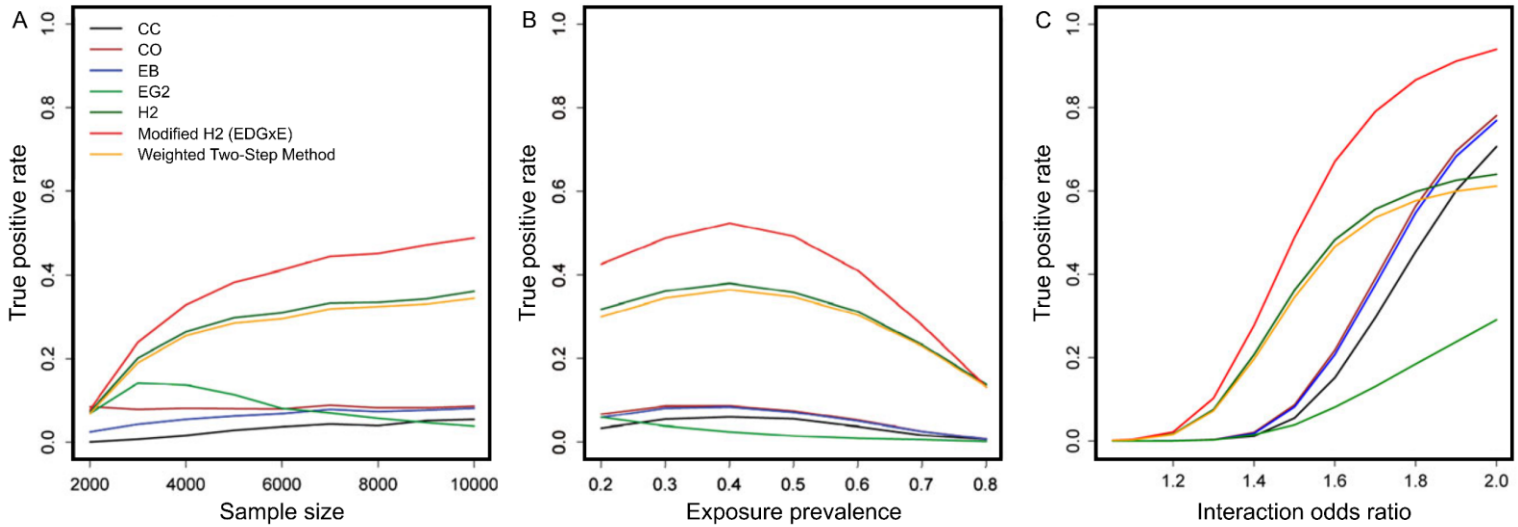
Each estimate of power is based on the proportion of 2,000 replicate datasets for which the indicated procedure achieved statistical significance for GxEs at the disease susceptibility loci. [a]Each model varies the indicated parameter from the base model setting. All results are based on the sample size of 3,500 cases and 3,500 controls and a total of one million SNPs. The highest estimated power for each analytical model is shown in bold type. [b]The base model has OR_G=1.2, OR_E=1.2, OR_{GxE}=1.5, q_A=0.23, p_E=0.40, initial bin size B=5 SNPs, no associations between disease susceptibility loci and environmental factors, no additional SNPs with DG associations or EG correlations. [c]OR between disease susceptibility loci and environmental factors. [d]Number of non-disease susceptibility SNPs simulated to have EG correlations in a source population. [e]Number of non-disease susceptibility SNPs simulated to have DG associations (but no GxEs). NA, not applicable because the type 1 error rate is inflated.



Reference Figure R1. Power to detect GxEs across a range of magnitudes for the marginal genetic effect for several analytical methods. The figures illustrate the statistical power for testing GxEs across a range of marginal genetic effects for several exhaustive scans and two-step methods, with 3,500 cases and 3,500 controls. (A) Moderate interaction with common genetic and environmental factors (OR_{GxE}=1.5, q_A=0.23, p_E=0.40). (B) Strong interaction with less common genetic and environmental factors (OR_{GxE}=2.0, q_A=0.13, p_E=0.10).



Reference Figure R1. Continued



Reference Figure R2. True-positive rate to detect GxEs in relation to the disease prevalence, exposure prevalence, and OR_{GxE} for several analytical methods. The figures illustrate the true-positive rate to detect interactions in relation to the disease prevalence, exposure prevalence, and OR_{GxE} for several exhaustive scans and two-step methods. The alternative hypothesis of a present interaction was simulated for 9,000 SNPs at different settings. (A) The number of cases was kept constant to 1,000 individuals; the number of controls was increased from 1,000 to 9,000 individuals. All other parameters were kept constant (OR_{GxE}=1.5, p_E=0.30). (B) The alternative hypothesis was simulated at different exposure prevalence. All other parameters were kept constant (n=10,000, OR_{GxE}=1.5). (C) The true-positive rate to detect GxEs was estimated at different interactive ORs. All other parameters were kept constant (n=10,000, p_E=0.30).

Abstract in Korean

이상지질혈증 및 고혈압에 대한 전장유전체에서의 유전자-환경 상호작용 연구: 흡연 및 음주, 비만을 중심으로

서울대학교 보건대학원

보건학과 유전체역학전공

강 문 일

인간의 형질 및 복합질환은 유전적인 요인과 환경적인 요인, 두 요인 간의 상호작용으로부터 영향을 받는 것으로 알려져 있다. 한국인에게서 가장 흔한 만성질환임에도 불구하고, 지금까지 한국인을 대상으로 한 이상지질혈증 및 고혈압에 대한 유전자-환경 상호작용 연구는 활발하게 이루어지지 않았다. 유럽계 인종을 중심으로 한 대규모의 전장유전체 연구로부터 지질 및 혈압과 연관된 유전변이가 각각 500개, 800개 이상 발견되었음에도 불구하고, 이를 통해 설명할 수 있는 각 형질의 유전율은 기대보다 낮았다. 따라서 본 연구는 한국인의 역학자료를 사용하여 이상지질혈증 및 고혈압과 연관되어 있는 유전자-환경 상호작용을 전장유전체 수준에서 검정하고, 이를 통해 추가적으로 설명할 수 있는 각 형질의 유전율을 제시하는 것을 목표로 한다. 유전요인과 환경요인 간의 상호작용을

연구함으로써 이상지질혈증 및 고혈압과 같은 복합질환의 생물학적인 기전을 이해하고, 더 나은 예측모형을 개발할 수 있을 것이라 기대한다.

이상지질혈증 및 고혈압에 대한 전장유전체에서의 유전자-환경 상호작용 연구를 수행하기 위하여 한국인유전체역학조사사업으로부터 총 18,025명의 대상자를 선별하였다. 이상지질혈증 및 고혈압은 각 질환의 임상진료지침에 제시된 진단기준에 따라 정의하였고, 흡연 및 음주, 비만과 같은 환경요인 또한 일반적으로 사용되고 있는 기준에 따라 정의하였다. 유전요인의 경우, 총 3,914,038개의 단일염기다형성에 대하여 각각의 유전자-환경 상호작용을 검정하였으며, 이를 위해 현재까지 개발된 분석모형을 최대한 다양하게 적용하였다. 모든 분석 결과는 지역사회기반코호트로부터 검정된 이후에 도시 및 농촌기반코호트를 통해 재확인되었으며, 최종적으로 확인된 유전자-환경 상호작용을 통하여 추가적으로 설명할 수 있는 각 형질의 유전율을 제시하였다. 이러한 연구 결과를 지질 및 혈압에 대한 유전자-환경 상호작용 연구 결과와 비교하여 제시하였다.

이상지질혈증에 대한 유전자-환경 상호작용 연구를 통하여 약 20개의 유전자-비만 상호작용을 확인하였다. 본 연구의 결과는 두 개의 새로운 유전자(*SCN1A*, *SLC12A8*)와 기존의 전장유전체 연구로부터 지질과 연관된

것으로 보고되었던 유전자(*APOA5*, *BUD13*, *ZNF259*, *HMGCR*)를 포함한다. 또한 새롭게 발견된 유전자-비만 상호작용을 통하여 각 지질의 유전율을 추가적으로 설명하였다. 중성지방의 경우, 유전자-비만 상호작용을 통하여 18.7%의 유전율을 추가적으로 설명할 수 있었다. 고혈압에 대한 유전요인과 환경요인 간의 상호작용 연구를 통하여 총 24개의 유전자-환경 상호작용을 확인하였다. 본 연구의 결과는 지금까지 보고되지 않았던 두 개의 유전자(*BRAP*, *SH2B3*), 혈압 및 비만과 연관된 유전자(*ATP2B1*, *ST5*), 그리고 기존의 전장유전체 연구로부터 음주와 연관된 것으로 보고되었던 유전자(*ALDH2*, *CUX2*, *HECTD4*, *MYL2*, *OAS3*)를 포함한다. 이러한 유전자-환경 상호작용을 고려할 경우, 약 0.3-2.1%의 유전율이 추가적으로 설명되는 것을 확인하였다. 지질 및 혈압에 대한 유전자-환경 상호작용 연구를 통하여 *APOA5*, *BUD13*에 위치한 네 개의 유전변이가 비만요인과의 상호작용을 통하여 중성지방에 영향을 준다는 것을 확인하였고, *TSPAN5*에 위치한 유전변이가 음주요인과 상호작용을 하여 수축기혈압에 영향을 준다는 것을 확인하였다.

본 연구를 통하여 특정한 유전요인을 가진 인구집단의 경우에는 흡연 및 음주, 비만요인이 정상적인 범주에 속함에도 불구하고, 이상지질혈증 및 고혈압 발생에 취약할 수 있다는 것을 확인하였다. 또한 유전자-환경 상호작용을 통하여 각 형질의 유전율을 추가적으로 설명할 수 있다는 것과

유전자-환경 상호작용과 연관된 단일염기다형성의 빈도가 인종별로 다르게 나타나는 것으로부터 각 인종별로 이상지질혈증 및 고혈압의 발생 위험도가 다를 수 있다는 것을 확인하였다. 본 연구를 통하여 새롭게 확인된 유전자-환경 상호작용은 인구집단을 각 질환의 고위험군 및 저위험군으로 구별하여 각 위험군에 특화된 임상진료지침을 제시하거나 맞춤의학 및 정밀의료를 실현하기 위한 하나의 근거로 사용될 수 있을 것이다.

주요어: 이상지질혈증, 고혈압, 흡연, 음주, 비만, 전장유전체, 유전자-환경 상호작용, 유전율, 메타분석

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